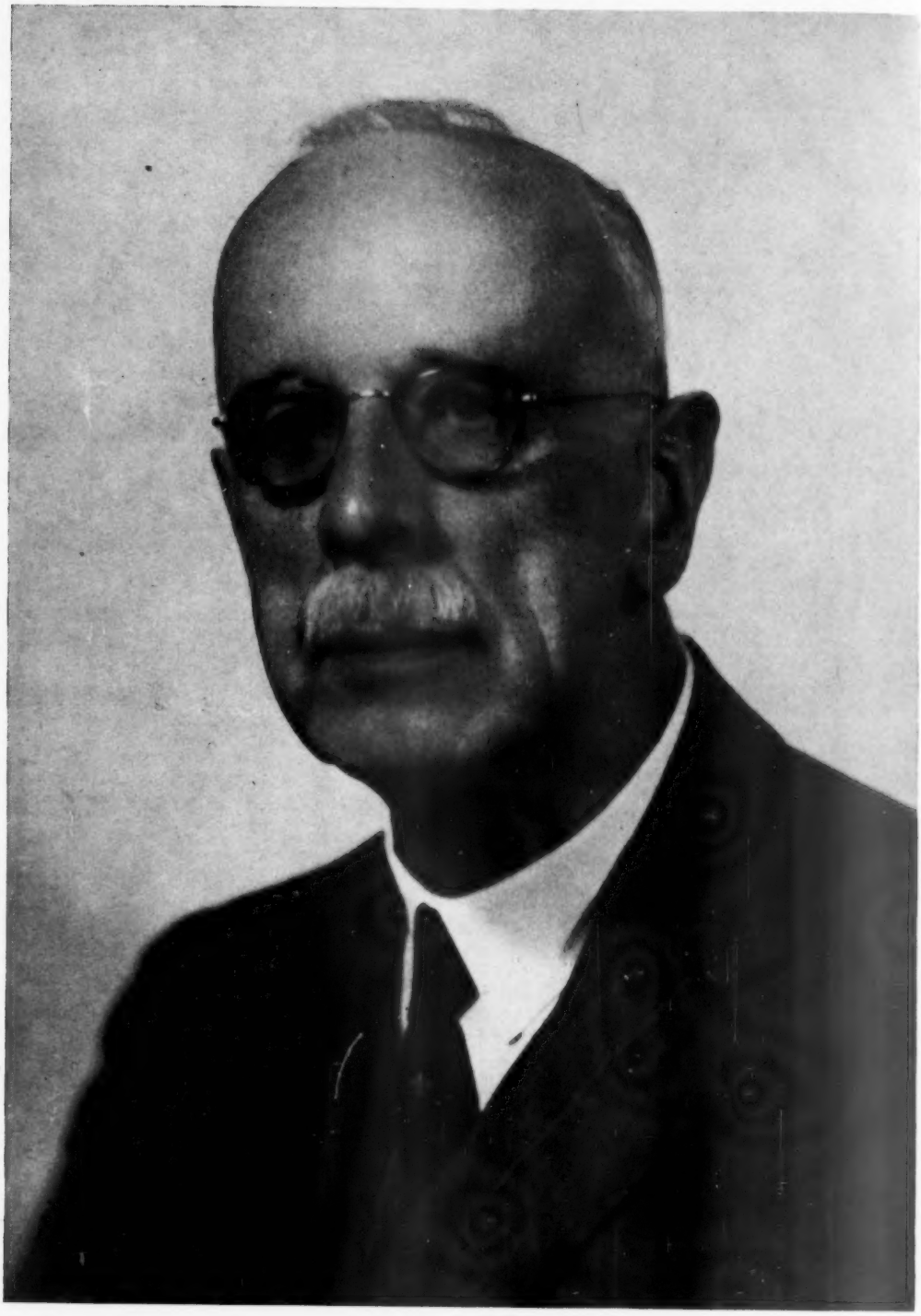
ANNALS OF THE RHEUMATIC DISEASES



C. W. BUCKLEY

[*facing p. 185*

EDITORIAL

This quarter has seen two anniversaries which are notable in the history of rheumatology. Both Dr. J. van Breemen and Dr. C. W. Buckley—respectively the father of the International League and the doyen of British rheumatology—have safely achieved their eightieth birthday. All readers of the *Annals* and all others interested in this field of medicine will wish to congratulate them! Plans are maturing in Holland to mark the first of these events by the foundation of an International Centre in Amsterdam for the Study of the Rheumatic Diseases, which has long been Dr. Van Breemen's dearest ambition. Further comment will be postponed until a later issue of this *Journal*, when this excellent project is further advanced.

Our own Dr. Buckley, it will be remembered, sponsored the four annual "*Reports on the Chronic Rheumatic Diseases*", issued by the pioneer rheumatism committee of the Royal College of Physicians from 1934 onwards. These "Reports" were subsequently transformed under his editorship into the *Annals of the Rheumatic Diseases* in its present form. Since he only vacated the editorial chair of this *Journal* at the end of last year, any success which it has achieved in the world at large must be attributed to his industry and learning. He was recently entertained to a dinner at which Lord Horder spoke eloquently of his professional virtues. Such is Dr. Buckley's personal modesty that he has forbidden further public tribute being paid here to his life and works, but it is fitting that his portrait should adorn this number of the *Journal* which he has so successfully fathered.

ANKYLOSING SPONDYLITIS: A SURVEY

BY

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It is appropriate that this number of the *Annals of the Rheumatic Diseases* should contain a survey of the recent work on that disorder known variously as Ankylosing Spondylitis, Rheumatoid Spondylitis, Marie-Strümpell's Disease, von Bechterew's Disease or Pelvo-spondylitis Ossificans; appropriate in that few in this country have given as much time to its study and as much attention to the problems it poses as Dr. C. W. Buckley of Buxton. For the past 25 years or so he has contributed steadily to our knowledge of this disease (Buckley, 1931, 1932 1934, 1935, 1936, 1938a,b, 1940, 1943, 1945, 1948a,b). In his first communication (Buckley, 1931), he reported 150 cases of various types of spondylitis and emphasized that von Bechterew's disease and Marie-Strümpell's disease were not two separate disorders, as had been claimed, but one disorder, that known now as ankylosing spondylitis, then as spondylitis deformans. At this time he emphasized the importance of preventing hip ankylosis and spinal kyphosis. In 1943 he drew attention to a useful diagnostic feature, the absence of compensatory increase in the normal lumbar curvature in ankylosing spondylitis as compared with its presence in adolescent kyphosis, a disease with which spondylitis had previously been confused. In the light of the recent papers by Romanus (1953) and Ford (1953), it is to be noted that he made a distinction between ankylosing spondylitis and the syndrome following genito-urinary infection, stating:

> If the hands or feet are affected before or simultaneously with the spine the diagnosis is not ankylosing spondylitis but infective arthritis, possibly of gonococcal origin affecting the spine (1943).
>
> Gonorrhoeal arthritis may undoubtedly attack the spinal articulations but in such cases other joints are usually affected earlier, and the regular centrifugal progress as well as some other characters are absent (1948).

He opposed (1943) the idea that ankylosing spondylitis was merely a spinal variant of rheumatoid arthritis on the grounds of the different sex ratio, the tendency to bony ankylosis, the centrifugal spread, and the failure to respond to gold therapy. Most workers in the United Kingdom still feel now as he did 10 years ago.

So many different views are still held on the nomenclature, aetiology, pathology, classification, and treatment of ankylosing spondylitis, that, even confining oneself to Great Britain, few dogmatic statements are possible. Most workers in this country consider ankylosing spondylitis a rheumatoid disorder, but more than a simple variant of rheumatoid arthritis; until more critical diagnostic tests are elaborated over the whole field of rheumatoid disease there seems little point in assuming an identical but unknown aetiology for two disorders, particularly when points of difference outweigh points of similarity. Buckley's four essential points of difference are still valid; radiological differences are obvious, and the differential sheep cell agglutination test (Rose and others, 1948; Ball, 1952; Svartz and Schlossmann, 1950; Foz, Batalla, and Barcelo, 1951), while giving positive results in some 40-90 per cent. of cases of rheumatoid arthritis in different series, only very rarely gives a weak positive reaction in a true case of ankylosing spondylitis. On histological grounds Van Swaay (1950, 1951) considers the disorder a different one, as Forestier and others (1951) affirmed on clinical grounds in their paper presented at the European Conference on Rheumatic Disorders. This argument will continue indefinitely until the aetiology of rheumatoid disease as a whole is better understood and until more exact diagnostic criteria are evolved. In the meantime, it is, perhaps, more profitable to study these disorders as different unsolved problems rather than to put them all into one diagnostic cauldron. In the study of the distinctive differences of the individual disorders more may be learnt of rheumatoid disease as a whole.

Family History.—There has been considerable interest in the incidence of positive family histories in this disorder. Hersh and others (1950) observed the pattern of inheritance in fifty families and concluded that ankylosing spondylitis could be attributed to an autosomal dominant factor, with about 70 per

cent. penetrance in the male and 10 per cent. in the female. Ankylosing spondylitis has been reported in two pairs of fraternal twins (Campbell, 1947; Rogoff and Freyberg, 1949) and in sisters (Fraser, 1950). Mason (1951) reported an unusual family where three members were certainly and three probably affected. Böni and Hautmann (1950), Tegner and Lloyd (1949), Blécourt (1951), and other authors comment on the familial incidence, and Parr and others (1951) recorded a significant family history in 11 per cent. of their cases.

Pathology.—Collins (1949) and Boland (1953) give what may be called the orthodox view of this disorder: an inflammatory condition of the sacro-iliac joints, the apophyseal joints of the spine, and the costovertebral articulations, with infiltration of lymphocytes and plasma cells and synovial membranous proliferation, the same changes as occur in the peripheral joints in rheumatoid arthritis. Granulation tissue growing out from inflamed synovial membrane invades the articular cartilage, eroding and destroying it, and the joint space becomes filled with fibrous tissue with eventual bony fusion. Van Swaay (1950, 1951) points out from how relatively few papers this account has grown and on what a small amount of pathological material it is based. As a result of careful study of the vertebral columns of three cases he came to the conclusion that in the spinal articulations no synovial proliferation and no cellular infiltration or vascularization occurred. The pathological process he considered distinctive and unlike that of rheumatoid arthritis, in that the joint was obliterated by new cartilage proliferating to replace the old, all joint space being destroyed by this new growth, and calcification then occurring to give bony fusion. Cruickshank (1951) obtained material taken from hips, sternoclavicular joint, knees, and sacro-iliac joints in this condition, in nine cases at operation and in three at autopsy. He found a process similar to that seen in rheumatoid arthritis but with a greater tendency to haemorrhage, a more marked and frequent thickening of small vessels and a greater tendency to bony fusion. He did not, from the evidence of his material, think that the assumption of the unity of the two diseases was warranted on histological grounds. In this issue Engfeldt, Romanus, and Ydén (1954) report details of one autopsy and several biopsy specimens; inflammatory changes were seen in some of the biopsy material, but not in the autopsy specimen where the disease had been present for some 30 years.

Clinical Picture.—The clinical picture is sufficiently well known to need no fresh description, but certain small signs have been commented on and may therefore be mentioned. Tenderness over the ischial tuberosities, iliac crest, and many other bony points is a very frequent finding (Hart and others, 1949), and may even bring the patient to the clinic. This bony tenderness may persist for weeks, months, or more rarely years; one of our patients habitually carries a small cushion as a protection for his tender ischial tuberosities. This bony tenderness may need local therapy and may mislead the diagnostician, for the punched-out areas seen in *x*-ray photographs may be mistaken for tuberculous disease if in an abnormal site such as the shoulder, or the vertebral body. Involvement of the sternomanubrial joint has been described by Savill (1951), Solovay and Gardner (1951), and Françon and others (1953). Davis and Blair (1950) emphasize the frequency of calcaneal periostitis or spurs in this condition. Hart and others (1950) emphasized the frequency of intercostal respiratory restriction as a prominent and diagnostic physical sign.

As regards peripheral joint involvement, figures vary immensely in different publications, perhaps partly because of different follow-up periods. Parr, White, and Shipton (1951) noted a peripheral onset in six of one hundred cases, Kuhns (1951) in 6·5 per cent. of two hundred cases, and Hart (1954) in 24 of 184 cases (13 per cent.). Forestier and his colleagues (1949), in a review of 200 cases of ankylosing spondylitis, found that 78 per cent. of 36 female and 56 per cent. of 164 male patients had peripheral joint involvement at some stage of the disease process. Sharp and Easson (1954), in an informative and stimulating paper, noted that, of their 332 cases, 242 were considered to be typical cases of ankylosing spondylitis, 59 atypical, and 31 borderline, the atypical group showing more peripheral joint involvement and a greater incidence (12 per cent.) of the tendinitis and tendon nodules which are virtually non-existent in typical spondylitics. This group of patients with peripheral changes occurs in a greater or lesser degree in all series of cases, but appears to be more common in the United States of America than in the United Kingdom (Glyn, 1953).

Iritis and iridocyclitis appear to be relatively common in ankylosing spondylitis, Buckley (1948a) giving 10 per cent. as the approximate incidence; it is clear (Hart, 1951) that the older the group of spondylitics studied the higher the incidence will be, the number of observation years being greater. Iritis may occur during the course of the spondylitis or it may precede it (Chan and Sun, 1951). No case of scleromalacia perforans in a spondylitic has so far been published.

Radiological Changes.—*X*-ray changes in ankylosing spondylitis are described in many publications (Scott, 1939; Forestier, 1939; Rolleston, 1947; Knutsson, 1950, 1953; Mowbray, Latner, and Middlemiss, 1949; Boland, 1953; Boland and Shebesta, 1946). There are, however, some recent observations of considerable interest. Guest and Jacobson (1951) drew attention to the lesions in bone, both extra- and intrapelvic. Oval zones of porosis, irregular bone margins with whiskery outgrowths, and occasional bitten-out areas into soft tissues, occur commonly in the pelvis on its outer aspect, but not on its inner margin which is free from muscle insertions. These authors found that 74·4 per cent. of the ninety patients studied had such lesions, commonly in ischial tuberosities and iliac crests. Extrapelvic lesions of this nature are not so readily recognized, and if in the vertebral body or humeral head may be mistaken for tuberculous lesions. Hamilton (1949) and Hart, Bogdanovitch, and Nichol (1950) reported on the radiological features of thoracic rigidity, the last-named using double-exposure films which showed restricted rib excursion but full or excessive diaphragmatic movement. This thoracic rigidity is a peculiar feature of ankylosing spondylitis and the double exposure film in expiration and inspiration is an easy way of demonstrating it radiologically.

Therapy.—The therapeutic pendulum has to-day swung away from emphasis on rest and fusion in a good position to a programme of much greater activity. The plaster shells and weeks or months of bed rest popular some years ago proved too productive of fixed hips and generally gave poor results (Swaim, 1939). Although many centres still use supporting jackets, many workers have largely or entirely abandoned them (Wyatt, 1945; Hart and others, 1949; Sharp and Easson, 1954) and have substituted for them exercises and postural drill. Edström (1952), for instance, advises back stretching and extension exercises thrice daily. Various forms of physiotherapy may occasionally give symptomatic ease, but they may on occasion aggravate symptoms. Manipulation has little or no part to play in therapy, for it is generally considered to be contraindicated in the treatment of spinal stiffness, and in the bed-fast osteoporotic subject fractures readily occur on manipulation of the hips.

Butazolidin (phenylbutazone) is a useful drug in ankylosing spondylitis, both in the early acutely painful phase and also later in the disease course; indeed, it is one of the most useful drugs for the fused spondylitic, who, with advanced crippling disease, still experiences much pain. Unfortunately in many cases the effective dose is also the toxic dose, and spondylitics, as a class already prone to dyspepsia and peptic ulceration (Hart and others, 1954), frequently show signs of gastric intolerance within a few days of starting the drug. Nevertheless, if it can be tolerated it is a useful analgesic and superior to simpler remedies because of its more prolonged action. Its other toxic side-effects, oedema, skin-rashes, buccal mucosal ulceration, haemorrhagic diathesis, etc., are much less common, and agranulocytosis is extremely rare.

Cortisone and ACTH are both useful in the treatment of acutely painful exacerbations (Hart, 1952), and cortisone is also of use in the prolonged suppressive treatment of the occasional patient who continues to deteriorate while on other therapeutic measures. Short-term hormone therapy may also be given as part of a programme of rehabilitation or to facilitate the administration of other forms of treatment. West and Newns (1954) treated six patients with ACTH for periods of from 1½ to 2 years. They concluded that prolonged adrenal stimulation was justified only in the most severe cases.

Deep *x*-ray therapy has been well discussed in excellent articles by Richmond (1951), Desmarais (1953), and Scott and Easson (1954). This form of therapy gives more lasting results than any other, its effect lying essentially in pain relief as the range of spinal movements is little affected in any but early cases.

Surgery.—On the whole surgery has a very restricted part to play in this disease. Operations on the hip are less satisfactory than in other rheumatic disorders, though Girdlestones or Batchelor's pseudarthrosis, or a Smith-Petersen's cup arthroplasty may help the individual carefully selected case. Revision operations are not uncommon in cup arthroplasty, but they cannot be done in the pseudarthroses. Lumbar wedge osteotomy is a useful operation for the severely kyphotic patient.

Summary

It is impossible to summarize this short survey. No attempt has been made to cover differential diagnosis, complications, or prognosis, nor to discuss in detail any particular aspect of the disorder. An attempt has merely been made to point to certain of the more interesting recent findings and observations, and to re-emphasize the indebtedness of all of us to that pioneer in this field of study, Dr. C. W. Buckley.

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HISTORY OF THE USE OF COLCHICUM AND RELATED MEDICAMENTS IN GOUT

WITH SUGGESTIONS FOR FURTHER RESEARCH

BY

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This brief history of the use of extracts of *Colchicum autumnale* in the treatment of gout had its origin in some research relative to the metabolism and mode of action of colchicine. It was interesting to review this history in order to develop a background, and thus to learn what ancient authorities and later observers knew about this drug. We shall review the evidence for the identity of certain plants thought by many investigators to be identical with our modern *Colchicum autumnale*, and which were described by early writers as poisons and later recommended in the treatment of gout; re-emphasize knowledge which has been more or less forgotten but which could be of experimental and practical usefulness to-day; delineate the fluctuations of popularity of colchicum as a treatment for gout during the past 1,500 years; and briefly mention the history of its uses in other fields of research. At the present time colchicine and its derivatives, as well as other mitotic-arresting drugs, are of considerable importance in the field of cancer research. More thoroughly established, however, is the role of colchicine in the treatment of acute attacks of gout, and it is this latter role that concerns us most here.

In the preparation of this study we have received invaluable assistance from Professor William H. Stahl, Chairman of the Department of Classics of New York University, who translated some of the Greek and Latin of the original manuscripts; and from the Inaugural Dissertation of Doctor Kurt Rüegg of Basel (Rüegg, 1936), on which we have relied heavily for our discussion of the mediaeval period. A résumé by Sharp (1909) has also been of some help, as has the work of Schnitker (1936).

The Drug Colchicine

To-day, in the treatment of acute attacks of gout, colchicum is administered as the relatively pure colchicine. The original structural formula elucidated by Windaus (1924) has been shown to be incorrect. The formula proposed by Dewar (1945), where colchicine contains a tropolone ring system is now accepted and has received experimental justification (Arnstein and others, 1948, 1949; Čech and Šantavý, 1949; Doering and Knox, 1951).

The drug is given by mouth in tablet form, 0·01 gr. each, at the onset of a gouty attack, and then every hour for five to ten doses until diarrhoea is induced. Usually at the onset of the diarrhoea the acute joint begins to resolve. In chronic gout some advocate its use in doses of 0·01 gr. once or twice a day over a prolonged period of time. Intravenous colchicine also has its advocates. Tinctures and wines of colchicum are to-day considered less desirable because of the possible variability in their drug content. The new hormones cortisone and ACTH have by no means usurped the ancient and useful position of this drug.

The mode of action of colchicine in gout is still a mystery. The most important known effect of colchicine, which is to inhibit the completion of mitosis or the division of cells, holding the process in what is called the metaphase, may or may not be related to the favourable effect of colchicine in an acute attack of gout. Proper spindle fibres necessary to normal cell division fail to develop. The chromosomes may divide in spite of the failure of cell division, thus giving rise to polyploidy or multiple sets of chromosomes. In larger doses not only do the dividing nucleii fail to produce the spindle but the chromatic material becomes pyknotic and degeneration of the cell proceeds.

The effect on mitosis is induced by 0·001 of the amount necessary to produce other observable metabolic effects on the cell, and its remarkably selective action is shown by the fact that the nuclear effects of other compounds are far less marked. To induce comparable effects with sodium cacodylate for example, one must use dosages a million times as great.

Anton Stoerck and others recognized a diuretic effect, and this has recently been investigated by

Dicker (1951). Hormone (Havas, 1938), enzyme, shock-like effects (Selye, 1949), and a reduction of vitamin C content of tissues, have all been postulated. Colchicine is moderately bacteriostatic (Gohar and Makkawi, 1951). It apparently has no effect on uric acid excretion. Its effect or lack of effect on uric acid metabolism awaits elucidation.

The unique poisonous effects of colchicine, of importance in this historical study, have been known since ancient times. There appear to be two distinct actions. First are the immediate irritating effects on gastro-intestinal tract, possibly by exciting the nerve endings to smooth muscle (Jacobj, 1890), but more likely through a central effect (Ferguson, 1952). Its action in this regard can be compared to that of muscarine, pilocarpine, and physostigmine. Secondly, colchicine, even in relatively enormous doses, produces a lethal effect slowly, requiring 3 to 6 hours to cause death in carnivora and longer in herbivora. This delay may be due, as in bacterial toxins, to a delay in absorption into the central nervous system (Dixon and Malden, 1908; Dixon, 1915) or, as Brues suggests (personal communication), to the possibility that the lethal action is associated with a metabolic factor such as the disappearance or accumulation of a critical metabolite. Death is apparently caused by vasomotor and respiratory paralysis. Hamsters do not succumb to colchicine poisoning (Orsini and Pansky, 1952).

Toxicity studies on poikilotherms, in whom the body temperature closely parallels the environment, show that these cold-blooded animals have remarkable tolerance to colchicine (Fuhrman, 1946), frogs requiring a dose of 100 mg. to 1 gram to prove fatal. However, the frog may be rendered much more sensitive by placing it in an incubator for a few days before the administration of the drug. Such preheated animals die with doses of 0·1 to 1 mg., but only after a delay of 2 to 5 days. The toxicity of colchicine in frogs was increased 400 to 500 times when the temperature was raised from 20° to 32° C. (Führer, 1913; Sanno, 1911).

The present-day supply of colchicine in the United States is derived mainly from botanical drug concerns who import the seeds and corms of the plant *Colchicum autumnale* from the temperate regions of Europe and from North Africa. This is due to economic factors, as our native corms should be just as productive. This material, received in a dry state, is treated with various solvents, more or less following the methods of extraction, purification, identification, and assay described in the U.S. Pharmacopeia. Further purification by chromatography can be accomplished by the method of Ashley and Harris (1944). Colchicine U.S.P. is said to contain 4 per cent. desmethyl-colchicine (Horowitz and Ullyot, 1952).

The Plant Colchicum

Colchicum autumnale is a perennial plant of the Lily family, to which belong *Lilium convallium* (Lily of the Valley) and *Veratrum* (*Hellebore*), the latter plants also being of some importance in this study. It is known popularly under many names, in English as Wild Saffron, Meadow Saffron, Autumn Crocus, Naked Lady, Naked Boy, and Son before the Father. In Central Europe it is called Herbstzeitlose and by many other names. It grows in most parts of the temperate areas of Europe, Asia, and America, at times growing wild in moist meadows.

The corm as obtained from the seed shops is a white, bulbous, mealy-like mass about 3 cm. wide by 5 cm. high, covered with a brownish red tunic. Below are the filiform roots. These corms are planted in September or October (Fig. 1*a*). Shortly thereafter new corms, one or more, develop along grooves in the old, and about the first frost these new corms send up a tube unaccompanied by leaves or seeds and produce a flower (Fig. 1*b*), usually lilac-coloured. Thus the name "Son before the Father" (the flower before the leaves and seed). The flowers last a few weeks and then fade and nothing is seen again until June, when the new corms send up many coarse, luxuriant, lanceolate leaves, about a foot long, and shortly thereafter the seed capsule (Fig. 1*c*). The old original corm has meanwhile been disintegrating. By mid-July the leaves and capsules wither and disappear, and by October the new corms are ready to go through the cycle again.

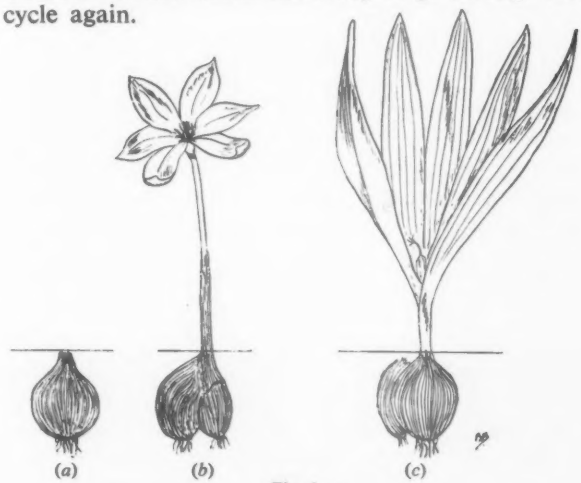

Fig. 1
(*a*) Bulb.
(*b*) Autumn flower from new bulb.
(*c*) Spring leaves from enlarged new bulb, the original bulb being now shrunken.

Colchicine is present in all parts of the plant, but particularly in the corm (0·35 per cent.), seeds (0·45 per cent.), and flowers (0·80-0·81* per cent.). The seeds are collected in June and July and the corms in July and August, or during flowering time, when they are considered to be the most rich in colchicine, although there is scant experimental evidence for this. Other plants known to contain colchicine are *Androcymbium gramineum* (Perrot, 1936), *Gloriosa superba* and species of *Merendera* (Mehra and Khoshoo, 1951), and *Gloriosa Rothchildiana* (Bryan and Lauter, 1951).

Colchicum autumnale may be confused with members of the Crocus family, particularly the Autumn Crocus, but it can be easily distinguished from them by the fact that the crocuses are of the Iris family, having three stamens, whereas the colchicums have six. *Colchicum autumnale* is only one of many colchicums. There are some thirty species of the genus (Krythe and Wellensiek, 1942), including a few spring-flowering varieties, all of which produce colchicine.

To use the terms Meadow Saffron or Saffron Crocus as synonymous with colchicum is confusing in that these terms suggest the *Crocus sativus*, a plant well known to the ancients, and described by Dioscorides, which has been throughout the ages the source of saffron, a medicinal drug, a perfume, a flavour, and a brilliant yellow dye. *Crocus sativus* is of the Iris family and has no relationship to the colchicums. It is still considerably cultivated in Spain and to some extent in America and England, but the large industry at Saffron Walden in England is a thing of the past (Bowles, 1924).

Nomenclature

In the history of colchicum four other terms continually recur: "Ephemeron", "Hermodactyl", "Surugen", and "Herbstzeitlose". The question is whether these are, or are not, synonymous. If not, what are the present names of the plants represented by these terms?

Ephemeron.—The extant records of the history of colchicum probably start with Theophrastus of Eresus (370-285 B.C.), the first botanist whose writings have come down to us, who, in his "History of Plants" under the term Ephemeron, described a poison with an effect which may be delayed for a considerable interval, thus probably explaining the derivation of the name. Theophrastus describes the plant as having leaves like the hellebore or lily, but gives no further botanical details.

Any relationship to colchicum probably would not have been considered were it not for the fact that Nicander (*c.* 150 B.C.) in his "Alexipharmaca", a work on plant poisons and their antidotes, also refers to ephemeron, again as a poison only.

> "Ephemeron", he says, is "that destructive fire of the Colchican Medea."

Thus the origin of the word colchicum, after the ancient district of Colchis on the Eastern shore of the Black Sea, a region associated in the Greek mind with all kinds of sorcery. Nicander's description of the baleful effects of his ephemeron is also not inconsistent with what one might expect from poisoning with colchicum. However, the effects of the poison used by Medea to avenge herself on her rival, at least as described by Euripides, do not suggest the action of colchicum. The Greek scholium to Nicander, written later, but at an undetermined period, states that "Ephemeron—is called Colchicon".

The "Materia Medica" of Dioscorides (1st-2nd cent. A.D.), as it has come down to us in the "Julianae Aniciae Codex", transcribed before 512 A.D. as a wedding present for the daughter of Anicius Olybrius, Emperor of the West, and now available in a photostat edition, speaks of "Ephemeron, which some call Colchicon", making the two terms synonymous. It then gives a description (on folio 105) of a poison which could very well be the modern colchicum.

> "Some call the plant Colchicon, others call it Bolbos. The Romans call it *Bulbus agrestis*. As the autumn is drawing to a close, the plant puts forth a whitish flower, like the flower of the Crocus. Later it bears leaves somewhat like those of the Bulbus, but shinier. It has a stalk a span long and reddish seeds; its root has a tawny skin verging into black. When peeled, the root is found to be white, tender, full of juice, and sweet. The plant has its diaphysis at about its middle, from which point it sends forth its flower. The plant is found chiefly in Messenia and Colchis. When eaten, it has a fatal effect by choking, as is the case with mushrooms. We have described the plant so that no one may confuse it with the edible Bulbus and eat it by mistake. It has a strange attraction for the unwary because of its pleasant taste. To those who have eaten of the plant, drinking cow's milk offers relief, as it does to those who have eaten poisonous mushrooms. Whenever there is cow's milk at hand, there is need of no other antidote."

The "Cheltenham Dioscorides Codex" [late 9th or early 10th cent.; original in Pierpont Morgan Library—Morgan MS. 652] confuses the issue by discussing two Ephemerons, the last (on leaf 311 verso) as an "Ephemeron which some call Agrestis iris", here describing an entirely different plant, which is "non-poisonous" and recommended for toothache and swellings.

In the English translation of Dioscorides (Goodyer, 1655; ed. Gunther, 1934), the terms are reversed, and the chapter on the poisonous variety begins "Colchicum, which some call Ephemeron". Gunther does not state the name of the Codex translated by Goodyer, but the illustrations are obviously taken from the "Julianae Aniciae Codex".

It is clear from the above that writers of the Dioscorides codices considered that there were two kinds of Ephe-

* These figures are variable and not constant.

meron, one "which some call Colchicon", probably the present-day colchicum, and another totally different, non-poisonous plant, apparently an Iris, recommended for toothache and tumourous swellings.

The section in the "Julianae Aniciae Codex" dealing with the "Ephemeron, which some call Colchicon", and that in the "Cheltenham Codex", are each accompanied by an illustration (Figs 2 and 3). These are fairly accurate representations of colchicum, but the plant is shown with leaves and flowers together, a phenomenon which does not occur with *Colchicum autumnale* or with the *Colchicum variegatum* of the Middle East. It may be a spring-flowering variety or the artist may have wanted to depict the various stages of the plant's growth in one diagram.

Scribonius Largus (*c.* A.D. 14-54) copied Nicander, adding nothing to the subject. Pliny the elder (A.D. 23-79) in his "Natural History", described the ephemeron, referring to it as the Iris agrestis of Dioscorides, and did not mention the poisonous ephemeron or colchicum. Galen (A.D. 131-201) speaks of "Ephemeron, not the poisonous plant which is also known by the name of Colchicum, but the other which is called Iris agria", and does not discuss colchicum itself either as a poison or as a drug. Aretaeus (2nd cent. A.D.), who wrote a most penetrating description of gout, says that "in gouty cases Hellebore is the great remedy". The leaves of hellebore or veratrum can be confused with those of colchicum. Aretaeus recommends the iris also, but does not mention either colchicum or ephemeron. Oribasius (4th cent. A.D.) copies Galen; he discusses the non-poisonous ephemeron, "not the poison which some call Colchicum".

Up to this point, then, it would appear that the ancients knew of a plant which they called "Ephemeron or Colchicum". It was poisonous and similar in its appearance and effects to the modern colchicum, and had for them no useful place in medicine. Another plant, also sometimes called ephemeron but never colchicum, is described as non-poisonous; it is sometimes called the *Iris agrestis* (Wild Iris), and was used in medicine for toothache and tumours.

Hermodactyl.—Alexander of Tralles (*c.* A.D. 550), in his "Therapeutica" made no mention of either ephemeron or colchicum. In his masterly discussion of gout, he recommended hermodactyl (Hermes for Mercury and dactylus, a finger) as a drug of choice. He gave no botanical description and its real identity is still a matter of dispute. He applied hermodactyl as we should colchicum to-day, giving it for gout, primarily for acute

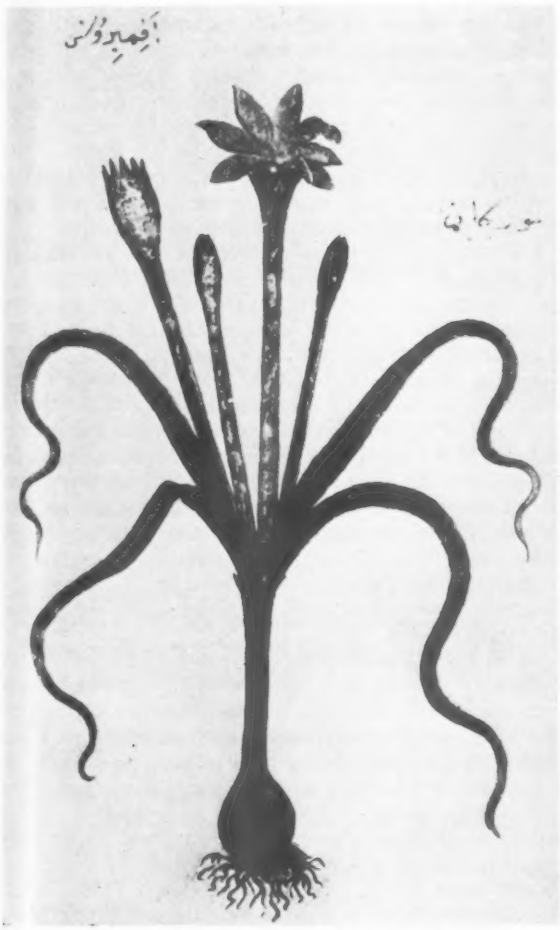

Fig. 2.—Ephemeron or Colchicon, from the Codex Julianae Aniciae, 104 verso.

Fig. 3.—Ephemeron or Colchicon, from the Cheltenham Codex. Plate 48.

attacks. The patients "declare that they get rid of their pain immediately because this medicine eliminates the toxic material with the stool movements, and the sick person can walk". He noted its cathartic effect, particularly warning against its irritating action on the stomach and intestines, and gave many prescriptions containing hermodactyl, preferably in pill form, with carminatives and cathartics added "in order to counteract the untoward effects on the gastro-intestinal tract". The evidence in favour of identifying hermodactyl with colchicum is first that the indications and effects appear similar, and second that Alexander does not once mention colchicum or ephemeron, a notable fact in that he was naturally familiar with the "Herbal" of Dioscorides.

Paul of Aegina (7th cent. A.D.), in his "Epitome", mentioned all the terms so far discussed: Ephemeron, "which some call Colchicum (because it grows in Colchis) or Bulbus silvestris", which is designated as a poison as in Nicander and Dioscorides; and again Ephemeron, "not the poisonous species but that which is called Wild Iris"; and lastly Hermodactyl, saying that "the root of it is possessed of purgative properties", and it is good "for affections of the joints in rheumatism", and bad for the stomach.

Paul of Aegina made a clear differentiation between the three terms so far discussed. In addition, he mentioned "recourse to preparations of Saffron", as distinct from the above three. We cannot be sure, however, whether Paul knew for a fact that all three were different, or whether he was merely copying from the texts of Dioscorides, Alexander, or others, without any personal knowledge of the subject. He himself admitted that he was not an original writer, but merely an eclectic.

References to colchicum and related terms in the Western world during the Middle Ages appear to be few. For example, Gilbertus Anglicus (1170-80? to 1230) refers to formulae called "Pilulae Artheticae Salernitorum", "Pilulae Arabice", etc., the active ingredient of which was a root he called hermodactyl.

Surugen.—The Arabic writers introduced a new term, "Surugen", with many variations of spelling. John Mesue (928-1018), in his "De re medicina libri tres" (Rüegg, 1936), spoke of "the Hermodactyl or Surugen", making the two synonymous. Mesue recommended it particularly for diseases of the joints and was the first to mention that the corm must be dried for 6 months before being used, fresh corms being "extremely poisonous".

Abu Mansur (10th cent. A.D.) spoke of "Surindschan" (Rüegg, 1936). Avicenna (980-1037) referred to "Hermodactyl or Surengian" and stated that it was a root with white or yellow flowers, was good for podagra, and, as recommended by Alexander of Tralles, was best given with carminatives and cathartics.

Other Arabic writers are mentioned by Rüegg (1936); Ibn-El-Beithar (1197-1248), for example, considered Hermodactyl and Surugen to be identical, but Serapion Junior (11th cent. A.D.) is most notable for our purpose because he made all the terms synonymous. Serapion said that "Surugen is Hermodactyl" and that "Hermodactyl, which is also called Achimeron" is similar to the Saffron, has leaves like the onion, a stem one span long, and a white root with a red cover, the root being soft, sweet, and toxic as mushrooms. He recommended cow's milk as an antidote (as did Dioscorides), and stated that it was used as a treatment for arthritis. Serapion, then, in making completely synonymous all the three terms so far discussed, is exactly contrary to Paul of Aegina. As far as we can determine he was the first to state (although it may have been common knowledge) that ephemeron or achimeron had a place as a medicine and not as a poison only, that it was valuable in the treatment of arthritis, and that it was synonymous with hermodactyl and surugen. His words were apparently unchallenged for the next 500 years, when he was attacked on this point, particularly by Euricius Cordus (see below).

At the same time hermodactyl, and not surugen, was still the term of choice in the Byzantine Empire. In a treatise on gout written for the Emperor Michael Palaeologus (*c.* 1282 A.D.) by Demetrius Pepagomenus, are prescriptions for hermodactyl pills, mixed with cathartics such as aloes and carminatives such as licorice or cinnamon, to render them "agreeable to the stomach".

Herbstzeitlose and Colchicum Autumnale.—By the time of the Renaissance a new term had appeared in Central Europe—"Herbstzeitlose", variously spelled and possibly meaning "without time" or "out of season", though many other derivations have been offered. It is a term which undoubtedly arose in the vernacular and was then gradually incorporated into the herbals. Botanical and medical writers soon began to use it as synonymous with the other terms discussed above.

Hieronymus Brunschwig (1450-1539), an Alsatian army surgeon, in his "Distillierbuch", for example, said that "wild saffron is the corm of Hermodactyl or Zeitlose". He followed Mesue in stressing the fact that it is dangerous if not dried long enough. The "Hortus Sanitatis" (Rüegg, 1936), a herbal with many wood-cuts, published in Mainz in 1485, made the problem appear quite simple by stating that the zeitlose was the hermodactyl of the Latins, the achimeron or colinticon of the Greeks, and the sturagen or Surumen of the Arabs, and that it was good for gout and dropsy and might be used externally with benefit in a number of conditions. Other authors, including Otto Brunfels (1488-1534), one of the fathers of botany, who wrote an "Herbarium or Lexicon of Medical Simples", also stated that these terms were synonymous.

A contrary opinion, however, may be seen in the writings of Euricius Cordus (1486-1535), a physician and botanist, who pointed out that Paul of Aegina put hermodactyl in a separate category from ephemeron and colchicum. Cordus thought that Serapion and many subsequent writers had erred in saying that these were synonymous terms.

Other early herbalists and botanists, and particularly students and translators of Dioscorides, attempted to identify these ancient terms (Rüegg, 1936). Thus, Caspar Bauhin (1550-1624), author of the famous "Pinax", said that hermodactyl and colchicum were identical. Leonhart Fuchs (1501-1564) thought the non-poisonous ephemeron

to be *Lilium convallium* (Lily of the Valley). Mattioli (1501-1577), the translator of Dioscorides into Italian, after receiving a specimen designated as hermodactyl from Constantinople, concluded that the hermodactyl of his age and of the ancients was not *Colchicum autumnale*, but *Orchis maculata* (Palmae Christi) or possibly *Iris tuberosa*. Carl Linnaeus (1707-1778), more or less following Mattioli, distinguished a *Hermodactyl verus*, and said it was probably an *Iris tuberosa* but "might be" the *Colchicum autumnale*.

Thus we see that the Arabs apparently accepted the opinion that the terms were synonymous, while during the early mediaeval period the Western world seemed silent on the subject. From the 15th century, however, the argument raged vigorously as to the identity of these terms. Unless new evidence is uncovered it seems doubtful whether the controversy will ever be settled. It is the author's opinion that the circumstantial evidence is in favour of the terms being identical.

The works of Alexander of Tralles (6th cent. A.D.) contain the first record of the use of colchicum in gout, assuming colchicum and hermodactyl to be identical. As hermodactyl, the drug, was used in gout in the Byzantine world, and as surugen it was used by the Arabic physicians. As hermodactyl it appeared in the earliest English literature, and as herbstzeitlose in that of Central Europe.

Administration in Gout

Renaissance Period and Later

During the Renaissance there were occasional references to these drugs as useful in gout. But in general the opinion had somehow arisen and was generally accepted in the Western world that they were extremely dangerous and even useless. Jaques Greven, for example, the translator of Nicander into French, wrote to Queen Elizabeth in 1568 that "this poison is the enemy of man's nature". Hieronymus Bock (1498-1554) in his "Kreutterbuch" said that it was dangerous and made the gout worse; Rembertus Dodonaeus (1517-1575) reported that it was poisonous and useless; Mattioli warned against its use internally. In spite of this reputation, however, it was obviously stocked by the pharmacies of the time, though its exact application in medicine is not clear. The commodity called hermodactyl appears to have been imported from the Orient, especially Constantinople, in spite of the fact that herbstzeitlose was common in the fields of Europe and England.

An idea of the poor opinion in which the drug was held may be gathered from a few examples from the 17th century. During this period such an eminent physician as Thomas Sydenham (1624-1689), who wrote one of the classic descriptions of gout, made no mention whatever of any of the possible names of this drug. He was opposed to the treatment of gout with drugs which acted on the bowel, but on the other hand recommended sassafras, elecampane, sarsaparilla, angelica, wormwood, opium, and others. Nor did Nicholas Culpeper (1681), in his famous "Herbal", mention this drug at all.

During the 18th century numerous medical books appeared with sections on gout and special dissertations on the subject (Lewis, 1761; Home, 1780; Blackmore, 1726; Hill, 1769; Cadogan, 1772; Heberden, 1802; and Kinglake, 1804), but none mentioned colchicum or hermodactyl. Horace Walpole wrote endlessly on gout and its treatment, but never on colchicum. Benjamin Franklin had gout himself and refers to its treatment, but makes no mention of the drug. Stephen Francis Geoffroy considered colchicum, Herbstzeitlosen knollen, and hermodactyl as all synonymous, but described their use only as magical amulets against epidemics.

On the other hand there were some exponents of the use of the drug, including Ambroise Paré (1517-1590), who made use of the "hermodactyl" in gout, Walther Hermann Ryff (1573), who said that the zeitlose was identical with hermodactyl and very useful in gout, and John Quincy (1733), author of the "Complete English Dispensatory", who looked on hermodactyl as a species of colchicum and called it, among other things, "the soul of the joints".

The London Pharmacopoeias of 1618, 1627, 1632, and 1639 listed "Radix Colchici s. Hermodactyl". However, the 1639 edition was the last to mention either colchicum or hermodactyl, and neither name appeared again for over 150 years, until in the 1788 edition colchicum was again listed (probably as the result of the writings of Stoerck (1764)), and hermodactyl was dropped forever. *Colchicum autumnale* was official in the Swiss Pharmacopoeia of 1771, and under the name of *Hermodactyl* it was official in the French Codex of 1761.

Modern Recognition of Colchicum

The modern era of the use of colchicum probably starts with Baron Anton Stoerck, who wrote a book on the use of *Colchicum autumnale* or Meadow Saffron in dropsical conditions and particularly in pleural effusions. Stoerck has been credited with the reintroduction of the use of colchicum for gout, but this is, as far as we can see, an error, in that Stoerck never applied the drug to the treatment of joint conditions. Its use in dropsy, already known to the Arabic physicians (see above), is most interesting in view of recent investigations into the diuretic effect of some mitotic-arresting drugs,

particularly colchicine. Later authors spoke highly of the synergistic action of digitalis and colchicine in the improvement of dropsical conditions, when digitalis alone failed to be effective (Hammond, 1861). Dicker (1951) has recently demonstrated on rats the water-eliminating action of colchicine.

The use of colchicum in gout was reintroduced, it appears to me, by Nicolas Husson, not a physician but a military officer in the French Army, who in the latter part of the 18th century concocted a panacea which he called "Eau Medicinale". This secret remedy had a great vogue in Europe and for many years its ingredients were the subject of controversy (Husson, 1783). The cases of gout described by the inventor are not so numerous as those of other diseases.

"Eau Medicinale" was introduced into England in 1808. There were a number of imitations, such as "Wilson's Tincture" and "Reynolds' Specific". Edwin Godden Jones (1810), said that "Eau Medicinale" had been discovered about 40 years earlier by Nicolas Husson, a military officer in the service of the king of France:

> "We are informed by himself that in the course of researches to which his propensity led him, he discovered a plant before unknown in medicine, which upon examination, was found to possess extraordinary virtues in the cure of various diseases."

From the beginning the concoction met with much opposition:

> "The clamours against it became at length so loud, that the sale of it was suppressed in Paris, in 1778, by an order from the police. This prohibition was removed on the fifth day."

Want (1814), after considerable experimentation and observation, stated that the main ingredient of "Eau Medicinale" was a venous infusion of colchicum corm; he called the attention of the medical profession to the influence of colchicum itself in the treatment of gout. Want was followed by other authors, such as Clark (1818). Sir Henry Halford (1831), thought highly of colchicum in gout, and, like Mattioli before him, sent to Constantinople for specimens of hermodactyl, and proved to his own satisfaction that they were identical with *Colchicum autumnale*. Home (1817), brother-in-law of John Hunter, and the man who, according to Garrison, burned Hunter's manuscripts and then used the material as his own original work, had gout himself, experimented with "Eau Medicinale" and colchicum and stated that colchicum was a "specific" remedy for gout and was the main ingredient of Husson's formula. To this Scudamore (1819), in his "Treatise on the Nature and Cure of Gout and Rheumatism" and other writings, somewhat reluctantly agreed, and from that time on the study and use of colchicum belongs to contemporary history.

The reintroduction of colchicum was attended by over-enthusiasm; thus, Haden (1820) and Maclagan (1852) gave a long list of asserted indications. The latter gives an extremely interesting and impartial survey on the subject, equal to his penetrating remarks on rheumatic fever. Moderation was again restored by the publication "The Nature and Treatment of Gout and Rheumatic Gout" (Garrod, 1859). Almost all our pertinent knowledge of colchicum is to be found in Garrod's classical descriptions. The only important aspect not known to Garrod was the drug's effect on mitosis. Garrod, like the ancients, recommended that a cathartic such as calomel be administered with colchicum.

Since Garrod's time very little of a positive nature has been added to our knowledge of the use and mechanism of action of colchicine in acute gout. Garrod (1848) had shown and verified that there was an increased amount of urates in the blood of gouty subjects, but that colchicum did not affect the blood level or excretion of urates. Theoretical explanations of its action (as an enzyme, as a hormone, as a "shock drug" acting through the pituitary-adrenal axis, or as inhibitor of uric acid synthesis) have been repeatedly proposed but without good experimental evidence. The attractive hypothesis that the mechanism of action in gout is in some way related to the phenomenon of mitotic arrest induced by colchicum is also without any support whatever.

Colchicum had been isolated by Pelletier and Caventou (1820). Geiger (1833) had extracted a fairly pure colchicum and called it colchicine. Zeisel (1883) elucidated the chemistry still further and worked out its empirical formula ($C_{22}H_{25}O_6N$). Houdès (1881, 1884) accomplished further purification. Jacobj (1890) wrote extensively of its properties. Šantavý and Reichstein (1950) have isolated four other colchicine-like substances from the seeds of the plant, but their properties are as yet unknown.

The history of the effect of colchicum and some 47 other chemicals (Krythe and Wellensiek, 1942) in inducing mitotic arrest has profound significance in cancer research, as well as in many other fields, such as endocrinology, genetics, and cytology, but this work is not within the scope of this summary. Of the 47 (which include acriflavine, podophyllotoxin, and auramine), colchicine is unique in that, as mentioned above, it acts in dosages far below the levels that would interfere with general cell metabolism. In suitable doses it inhibits only the metaphase. The literature on this subject is extensive

indeed, the bibliography of Eigsti (1947) taking up 48 pages.

Dustin and Grégoire (1933a, b) observed the effect of arsenical and other compounds on nuclear division in grafted mouse tumours. Lits (1934), working in Dustin's laboratory at the University of Brussels, reported on the general cellular reactions and "lesions" caused by colchicine in animal cells. Amoroso (1935) observed the beneficial effect of colchicine on the malignant growths of patients treated primarily to relieve acute attacks of gout and tested the efficacy of colchicine on malignant tumours in animals. Ludford (1936) reported on its action on normal and malignant cells *in vitro* and *in vivo*. He is credited with having pointed out that the inhibitory action of colchicine on mitosis is not at the onset, but in the metaphase. Any one microscopic slide will show an increased number of cells in mitosis, but this apparent stimulative effect, as first suggested by Dustin and his co-workers, was shown by Ludford to be merely an accumulation of the arrested cells. Ludford showed at an early date that the effective dose was unfortunately at or only just below the lethal dose. Havas (1937) and Gavaudan (1937) were the first to show the effect of colchicine on the germination of wheat seeds and the growth of seedlings, and the extent to which a parallelism can be found in this regard between animal and plant cells. Brues (1936), Brues and Marble (1937), Brues and Cohen (1936), and Brues and others (1940), investigated the effects of colchicine on the regenerating liver of the rat following partial hepatectomy, and used this observation to develop a method of measuring the anti-mitotic action of any particular drug. Allen and others (1936), working at the Yale Medical School, introduced these effects to endocrinologists, pointing out the application of the colchicine effect to hormone study and assay. The investigations in America culminated in the successful demonstration of polyploidy (chromosomal division without cell division) in plants by Blakeslee (1937), Blakeslee and Avery (1937), Nebel (1937), Nebel and Ruttle (1938), Eigsti (1947), and many others, and suggested the possibility of developing new species through the application of a drug like colchicine. The subsequent literature of colchicine and related compounds while voluminous (Eigsti, 1947) mainly centres in problems in other fields than that of gout.

The most recent significant advance in our knowledge of colchicum was the production of radioactive colchicine, randomly labelled with carbon C-14 by the biosynthetic procedures developed by Geiling, Kelsey, McIntosh, and Ganz (1948). This radioactive preparation was used by Back and others (1951) at the same laboratory to trace the fate of colchicine *in vivo*.

Suggestions for Future Investigations

A summary of useful suggestions that may be gleaned from this brief history appears to be worthwhile. It might be fruitful to investigate the effect of the other ingredients of colchicum corm, continuing the work of Šantavý and Reichstein (1950); the content of the corm at various times of the year; the content and type of drug present in fresh corms and in corms "dried over 6 months"; the effect of colchicum as a diuretic; a clinical trial of the conjoined use of carminatives and cathartics with colchicine, as was the custom with the ancients, rather than the administration of paregoric to allay the final diarrhoea as is at times the practice to-day; a re-investigation of the use in gout of hellebore (veratrum) which appears now to have a synergistic effect with colchicum; the application of colchicine locally for its effect on tumours (Nelson, 1951) and ulcers, and for its possible systemic effect in arthritis when locally applied (Carr, 1951); and the possibility of poisoning through prolonged administration in chronic gout. The metabolism and the mode of action of colchicine in gout is an open field for research.

Many references to the history of colchicum in current medical literature are erroneous and these errors have been carried over from article to article. We hope we have corrected some of these without adding others of our own.

Summary

The use of colchicum first as a poison and later in the treatment of gout can be traced back at least 2,000 years. The new hormones, cortisone and ACTH have by no means usurped the ancient and useful position of this drug.

The most important known effect of colchicum which is to inhibit completion of mitosis or the division of cells, may or may not be related to its favourable effect on an acute attack of gout. Other theories as to its mode of action in gout have been proposed, but without sufficient evidence to establish their validity.

The toxicology of colchicum is unique in that it produces its lethal effects slowly, requiring a number of hours to cause death in carnivora, and longer in herbivora. Some poikilotherms are practically immune to its toxic effects, unless artificially heated.

Colchicum autumnale L., from which colchicum is

obtained, is a perennial plant of the Lily family, and must not be confused with the Crocuses, which are of the Iris family and contain no colchicum.

It is probable that colchicum was known to the early Greeks under the term Ephemeron "which some call Colchicon". It was first referred to, and as a poison, by Theophrastus, and subsequently by Dioscorides, from whose "Herbal" two pictures of Ephemeron are reproduced in this text.

Alexander of Tralles (*c.* A.D. 550) in his "Therapeutica", made no mention of either ephemeron or colchicum, but recommended hermodactyl as the drug of choice. He gave no botanical description and the real identity of hermodactyl is in dispute. The reasons in favour of identifying hermodactyl with colchicum are first that the indications and effects appear similar, and second that Alexander does not once mention colchicum or ephemeron, a notable fact in that he was naturally familiar with the "Herbal" of Dioscorides.

The Arabic physicians introduced a new term, surugen, and later made all three terms synonymous. Serapion said that "Surugen is Hermodactyl" and that "Hermodactyl is also called Achimeron". The Arabs recommended this Surugen for the treatment of arthritis.

Meanwhile, in Central Europe, probably during the late Middle Ages, a new term—herbstzeitlose—developed, and this was recommended for the treatment of gout. The controversy as to the identification of herbzeitlose with ephemeron, colchicum, and surugen, which immediately arose lasted until the 19th century. The bulk of evidence appears to support the thesis that these terms are synonymous.

The use of these plants in gout underwent great fluctuations in popularity. As hermodactyl the drug was used in gout by the Byzantines, and as surugen it was used by the Arabs. As hermodactyl it appeared in the earliest English medical literature, and as herbstzeitlose in that of Central Europe. By the 15th century, however, its use in gout had fallen into great disrepute, because of the secondary toxic manifestations which physicians had difficulty in controlling. As a result almost all the physicians of the 17th and 18th centuries ignored colchicum in the treatment of gout.

The modern history of the use of colchicum in gout starts with Nicolas Husson, not a physician but an officer in the French Army, who concocted a panacea called "Eau Medicinale", the active ingredient of which was found to be colchicum. With the writings of Scudamore (1819) colchicum became the established treatment for acute attacks of gout. This opinion was supported by the elder Garrod, since whose time very little new has been learned about the administration or mode of action of the drug.

The effect of colchicum in arresting mitosis has been used experimentally in tumour research, starting with Dustin and his associates in 1933. This work has had profound significance in cancer research, as well as in many other fields, such as endocrinology, genetics and cytology.

A study of the history of colchicum brings to light many still unsolved problems related to its isolation, administration, and pharmacodynamics, and the metabolism and the mode of action of colchicum in gout is an open field for research.

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Histoire de l'emploi du colchique et des médicaments apparantés dans la goutte, avec des suggestions pour des recherches ultérieures

RÉSUMÉ

L'emploi du colchique—comme poison et plus tard dans le traitement de la goutte—remonte au moins à deux mille ans. Les nouvelles hormones, comme la cortisone et l'ACTH, n'ont nullement remplacé ce médicament utile et ancien.

L'effet du colchique le plus important qu'on connaisse, celui d'inhiber la phase terminale de la mitose ou de la division cellulaire, pourrait bien être lié à son effet favorable dans l'attaque aigu de goutte. D'autres théories existent sur son mode d'action dans la goutte, mais il manque de preuves suffisantes à leur appui.

La toxicologie du colchique est unique dans le sens que son effet mortel est lent, ne s'exerçant qu'au bout de plusieurs heures chez les carnivores et plus tard chez les herbivores. Certains animaux poïkilothermes sont en fait à l'abri de ses effets toxiques, à moins qu'on ne les réchauffe.

Colchicum autumnale, d'où vient le médicament, est une plante vivace de la famille des liliacées; on ne la confondra pas avec le crocus qui est un iridacé et qui ne contient pas de colchicine.

Il est probable que les Grecs anciens ont déjà connu le colchique sous le nom d'*ephemeron* "que certains appellent *Colchicon*". Le premier à en faire mention comme poison fut Théophraste, suivi de Dioscoride; c'est de l'"Herbal" de ce dernier que nous reproduisons dans le texte les deux figures d'*ephemeron*.

Alexandre de Tralles (550 apr. J.C.) dans "Thera-

peutica" ne fait mention ni d'*ephemeron* ni de colchique, mais recommande l'*hermodactyl* comme médicament de choix. Il ne donne pas de description botanique et l'identité de la plante qu'il décrit est en question. Deux raisons plaident en faveur de l'identité du *hermodactyl* et du colchique: tout d'abord les indications et les effets semblent similaires et, deuxièmement, Alexandre ne fait jamais mention de colchique ni d'*ephemeron*, ce qui est remarquable puisqu'il était censé de connaître l'"Herbal" de Dioscoride.

Les médecins arabes introduisirent un terme nouveau, *surugen*, et plus tard les trois termes devinrent pour eux synonimes. Serapion dit que "*surugen* est *hermodactyl*" et que "*hermodactyl* s'appelle aussi *Achimeron*". Les Arabes recommandèrent *surugen* contre l'arthrite.

En attendant, en Europe Centrale, probablement vers la fin du moyen âge, naquit un terme nouveau—*Herbstzeitlose*, recommandé contre la goutte. Une polémique concernant l'identité de *Herbstzeitlose*, *ephemeron*, *surugen* et colchique commença bientôt et se prolongea jusqu'au XIX-ème siècle. La plupart des preuves semble supporter la théorie de leur identité.

La vogue de cette plante contre la goutte subit de grandes fluctuations. Les Byzantins l'utilisèrent sous le nom de *hermodactyl*, les Arabes sous celui de *surugen*. L'ancienne littérature médicale anglaise mentionne *hermodactyl*, et celle de l'Europe Centrale *Herbstzeitlose*. Au XV-ème siècle, cependant, son emploi contre la goutte tomba en désuétude en raison des manifestations toxiques secondaires que les médecins d'alors eurent peine à juguler. En conséquence, presque tous les médecins du XVII-ème et XVIII-ème siècle ignorèrent le colchique dans le traitement de la goutte.

L'histoire moderne de l'emploi du colchique contre la goutte commence avec Nicolas Husson, officier de l'armée française et non pas médecin, qui confectionna une panacée, *Eau Médicinale*, dont l'ingrédient actif principal, comme on l'a su plus tard, fut le colchique. Cette plante occupa le premier rang dans le traitement de l'attaque de goutte avec les écrits de Scudamore (1819), supporté par Garrod ainé. Depuis le temps de ce dernier on a ajouté très peu à nos connaissances de la posologie et du mode d'action du colchique.

Le pouvoir du colchique d'arrêter la mitose fut appliqué dans les recherches de laboratoire sur les tumeurs, inaugurées par Dustin et collaborateurs en 1933. Leur travail eut une grande importance dans les recherches sur le cancer ainsi que dans d'autres domaines, telles que l'endocrinologie, la génétique, et la cytologie.

L'étude de l'histoire du colchique met en relief les nombreux problèmes posés par l'isolement, la posologie, et la pharmacodynamie du médicament. Le métabolisme et le mode d'action du colchique dans la goutte offrent toujours un champ des recherches.

Historia del empleo del cólchico y de medicamentos aliados en la gota con sugestiones para investigaciones ulteriores

Sumario

El uso del cólchico—como veneno y luego en el tratamiento de la gota—se conoce desde al menos 2.000 años. Las nuevas hormonas, como la cortisona o la ACTH, no usurparon de manera alguna la posición antigua y útil de este medicamento.

El más importante efecto del cólchico que se conozca, el de inhibir la fase terminal de la mitosis o de la división celular, estaría quizás en relación con su efecto favorable en el ataque agudo de la gota. Fueron emitidas otras teorías sobre el modo de acción del cólchico sobre la gota, pero sin pruebas suficientes de validez.

La toxicología del cólchico es única en que su efecto mortal es lento, ejerciéndose tan sólo después de algunas horas en los carnívoros y todavía más tarde en los herbívoros. Algunos animales poiquilotermos no sufren practicamente sus efectos tóxicos a menos de calentarlos.

Colchicum autumnale del cual viene el medicamento, es una planta vivaz de la familia liliácea, que no se debe confundir con el azafran que es un iridáceo.

Es probable que los griegos antiguos conocieron el cólchico con el nombre de *ephemeron* "que algunos llaman *Colchicon*". Primero a mencionarle, como veneno, fué Teofrasto; le siguió Dioscorides, de cuyo "Herbal" se reproducen aqui las dos figuras de *ephemeron*.

Alejandro Traliano (550 A.C.) en su "Therapeutica" no hace mención de *ephemeron* ni de cólchico pero recomenda *hermodactyl* como medicamento de elección. Faltando la descripción botánica, su identidad es opinable, pero existen dos razones en favor de la tesis que *hermodactyl* y cólchico son idènticos: las indicaciones y los efectos parecen similares y, además, Alejandro nunca menciona el cólchico o el *ephemeron*, hecho notable ya que naturalmente conocía el "Herbal" de Dioscorides.

Los médicos árabes introdujeron un término nuevo, *surugen*, haciendo sinónimos los tres términos. Serapion dijo que "*surugen* es *hermodactyl*" y que "*hermodactyl* se llama también *Achimeron*". Los árabes recomendaron *surugen* para artritis.

Entretanto en Europa Central, probablemente hacia los fines de la edad media, nació un término nuevo—*Herbstzeitlose*, recomendado contra la gota. Una polémica respecto á la identidad de *Herbstzeitlose*, *ephemeron*, *surugen* y cólchico empezó muy pronto, prolongándose hasta el XIX siglo. La mayoría de las pruebas parece soportar la teoría de su identidad.

La boga de esta planta contra la gota sufrió grandes fluctuaciones. Como *hermodactyl* la emplearon los bizantinos y como *surugen* los árabes. La antigua literatura médica inglesa menciona *hermodactyl* y la de la Europa Central *Herbstzeitlose*. En el siglo XV, sin embargo, su empleo contra la gota sufrió descrédito a causa de manifestaciones tóxicas secundarias que los médicos tuvieron dificuldad en controlar. En consecuencia, casi todos los médicos del XVII y del XVIII siglo ignoraron el cólchico en el tratamiento de la gota.

La historia moderna del empleo del cólchico contra la gota empieza con Nicolas Husson, que no era médico sino oficial del ejército francés, quien confeccionó una panacea, *Eau Médicinale*; se supo más tarde que su ingrediente activo principal fué cólchico. Esta planta ocupó el primer lugar en el tratamiento del ataque de gota con los escritos de Scudamore (1819), soportado por Garrod mayor. Desde los tiempos de éste poco fué añadido a nuestros conocimientos de posología y del modo de acción del cólchico.

El efecto del cólchico de parar la mitosis fué aplicado experimentalmente en la investigación de los tumores, empezando con Dustin y sus colaboradores en 1933. Esta obra tuvo gran importancia en la investigación del cáncer así como en muchos otros dominios, como endocrinología, genética y citología.

El estudio de la historia del cólchico pone de relieve problemas que quedan por solver respecto al aislamiento, posología y farmacodinamia. Asimismo, el metabolismo y el modo de acción del cólchico en la gota abren un campo de investigación.

ZONE ELECTROPHORETIC STUDIES OF PLASMA PROTEINS IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS*

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This paper is a report of our investigations into the estimation of plasma proteins by zone electrophoresis; and the relationship between the level of the plasma fibrinogen and the erythrocyte sedimentation rate in patients with rheumatoid disease. The effects of various forms of treatment is also described.

Material

The material in this study consists of 172 zone electrophoretic analyses of plasma proteins; 23 from eighteen normal subjects and 149 from 25 patients suffering from rheumatoid arthritis or ankylosing spondylitis. Sixteen replicate analyses were carried out on serum obtained from one of the normal subjects. In addition, plasma fibrinogen levels were determined, by precipitation, on 173 occasions, in the patients and in fourteen of the healthy persons. Sedimentation rates were performed concurrently in all instances.

Twenty of the patients were diagnosed as having typical peripheral rheumatoid arthritis, four of these being children under the age of 12; one patient had pure ankylosing spondylitis, and four were suffering from spondylitis with peripheral joint involvement. All patients were hospitalized in the Arthritis Research and Treatment Centre, Regina General Hospital, under the auspices of the Saskatchewan Division of the Canadian Arthritis and Rheumatism Society.

The ages of the normal subjects varied from 19 to 45 years, and those of patients extended from 7 to 79 years. The sex incidence of the healthy persons was evenly divided and among the patients there were thirteen men and twelve women. None of the normal group was thought to have any concurrent illness. Amongst the patients, rheumatoid disease had been present for only 6 months in two cases, but five persons had been afflicted for more than 15 years. The average duration of arthritis was 4½ years. Most of the patients were in the more advanced stages of the disease.

Control studies were carried out on seven patients before the institution of any specific systemic therapy, and in seven others who received no specific medication throughout their hospitalization. The remaining patients had been receiving either hormonal, gold, or *x*-ray therapy at the commencement of the study or before admission.

Interest was aroused in the relationship between the erythrocyte sedimentation rate and the plasma fibrinogen levels in rheumatoid arthritis as a result of the work in Toronto of Fletcher and others (1952). These authors reported a very definite correlation between these two estimations, particularly when the plasma globulins were within the normal range.

It was felt of interest, therefore, to investigate this relationship further and to compare the sedimentation rate with fibrinogen levels estimated by both the precipitation method and by zone electrophoresis. The initial comparisons, in this study, showed no significant correlation, although after discarding cases with high globulins some relationship did seem apparent. It was then remembered that this linear relationship is frequently upset during therapy, particularly with cortisone or ACTH, because the elevated fibrinogen level decreases before, and more rapidly than, the sedimentation rate. This was shown very clearly by Fletcher and others, who also illustrated graphically the alteration in this fibrinogen-sedimentation rate correlation. With this in mind, scattergrams were made only of analyses from plasma taken from patients with normal globulin (less than 2·5 g./100 ml. plasma) during control periods, and from the normal subjects.

With regard to therapy during the study, three patients received gold or cortisone alone. Four patients were given cortisone at first to which gold therapy was later added. In three cases phenylbutazone was administered alone, and in four others this drug was used in addition to maintenance cortisone treatment. (The usual doses were 37·5-50 mg. cortisone and 200-400 mg. phenylbutazone.) One patient received *x*-ray therapy for ankylosing spondylitis.

* This study was assisted by a grant-in-aid from the Canadian Arthritis and Rheumatism Society.

Methods

The erythrocyte sedimentation rates were done by the Westergren method in duplicate on patients and single determinations on normal subjects.

The plasma fibrinogens were determined by two methods: first by that described by Campbell and Hanna (1937), in which the fibrinogen was precipitated with sodium sulphite, redissolved, and estimated photometrically according to the procedure of Gornall and others (1949); secondly, by the zone electrophoresis technique described below.

Total serum protein, albumin, and total globulin estimations were carried out by the precipitation-biuret method at least once on each control and each patient.

Complete protein fractionations were carried out, using the zone electrophoretic technique, a modification of that described by Flynn and De Mayo (1951), which is essentially a combination of the methods of Durrum (1950) and of Cremer and Tiselius (1950).

Apparatus.—The electrophoretic apparatus (Fig. 1A) was modified to consist of a methacrylate plastic box, 24 × 10″, with two buffer compartments, 10 × 1½″, at either end. The outer compartments contained the carbon rod electrodes and a filter paper bridge connected the two compartments. A glass plate, 17 × 10″, formed the filter paper support between the two inner compartments. The paper strips were placed across the support so that the ends dipped into the inner buffer compartments. A glass plate covered the entire assembly, being pressed down carefully on the paper strips.

Technique.—The paper strips, No. 1 Whatman, 2½″ wide, saturated with barbiturate buffer, *p*H 8·6, were stretched across the supporting plate with each end dipping into the buffer solution. Another filter paper strip was used to remove the excess solution from the area to which the plasma was to be applied. 0·10 ml. plasma was streaked across the paper to give a line about 1 cm. wide. The cover plate was then lowered into place, both plates having previously been coated with silicone grease to reduce absorption of the protein on the glass. The current was applied across the system at the rate of about 0·4 milli-ampères per centimetre width of paper for 6 hours. Three samples were run simultaneously. A D.C. power unit, producing up to 550 v., regulated, was required. The cover glass was removed, the ends of the paper trimmed off, and the strips air-dried overnight.

The staining procedure was exactly the same as that of Flynn and De Mayo (1951).

A densitometer, described below, was used to obtain the data from which the electrophoretic curve was plotted on graph paper. The curve of each fraction was drawn to overlap the next fraction at the minima between the two. The area for each curve was obtained by the method of counting the squares. The percentage of each fraction was obtained from its area in relation to the total area.

The densitometer, or scanning device, was constructed according to the description given by Griffiths (1952). It was built on a box, 22 × 12 × 4″, with two removable glass plates, 18 × 3″, covering a hole in the top 2½″ wide and extending the full length of the top (Fig. 1B, opposite). Above the glass plates was mounted a 100-w., white-light source, focussed through a slit 1½ × $\frac{1}{10}$″ in the base of the lamp-housing, the axis of the slit being at right angles to the length of the glass plates. Directly below the light source and connected to it with a bracket, a rectangular photo-electric cell was installed. The whole assembly moved above and below the glass plates by means of a screw moving $\frac{1}{10}$″ between each reading. The photo-electric cell was mounted in a black plastic box and the light source was protected by a sheet metal housing. The photo-electric cell was connected to a logarithmic type ohmmeter and the readings of this were recorded as relative density. When a pattern was to be read, the strip was placed between the glass plates and the density scale set at zero at a point on the strip

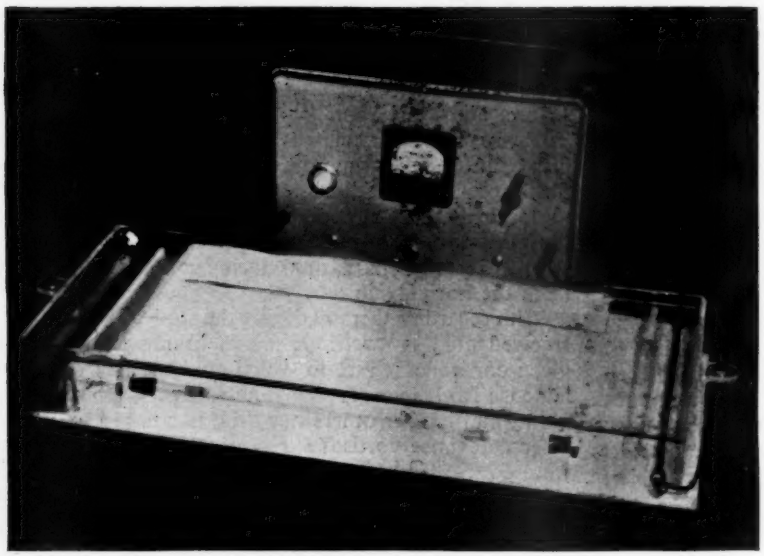


Fig. 1A.—Zone electrophoretic apparatus, showing plastic container with paper strips in position and power unit.

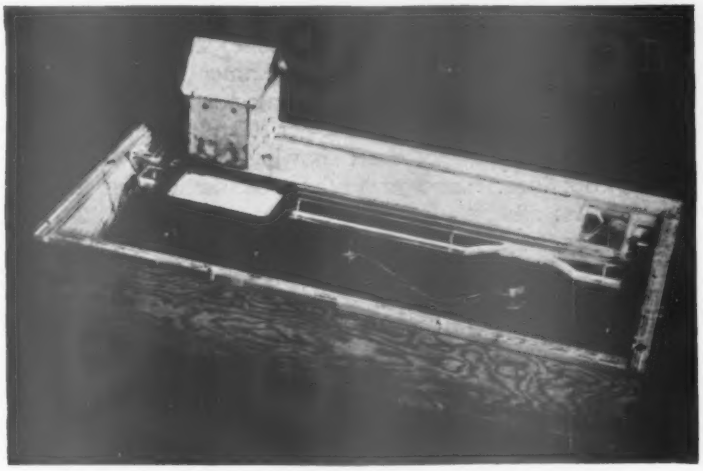


Fig. 1B.—Densitometer or scanning unit.

from which the dye was completely eluted. The readings then represented the relative optical density at $\frac{1}{10}$" intervals along the strip.

The necessary technical procedure to do six analyses required about 3 hours. The apparatus required no attention during the electrophoretic separation except the occasional adjustment of the current. This represents considerable reduction in time required for complete fractionation by salt-precipitation procedures.

A large number of the initial samples were quick-frozen for storage. This was found unsatisfactory since the fibrinogen tended to form a precipitate which did not redissolve on warming to room temperature. That difficulty was later avoided by the use of fresh samples only. None of the original material was included, therefore, in this report.

Observations

(a) Evaluation of Precision of Zone-Electrophoresis Technique.—Two samples of blood were obtained from one individual on consecutive days, and the serum separated and mixed. Sixteen replicate analyses were done on the serum on successive working days, the serum being stored in the refrigerator between analyses. Although the main part of the work in this report concerns plasma, serum was used here because it could be more satisfactorily stored. The results of these replicate analyses, including the mean values and the standard deviation, are given in Table I.

TABLE I

REPRODUCIBILITY OF ANALYSES ON ONE SAMPLE OF SERUM

(Per cent. of Total Protein)

Analyses ..	Albumin	Alpha-Globulin	Beta-Globulin	Gamma-Globulin
	81·5	5·3	8·8	4·4
	86·0	3·4	5·1	5·5
	88·5	3·9	3·5	3·5
	77·0	6·4	6·2	10·5
	82·5	3·5	6·4	7·5
	84·0	6·1	4·3	5·7
	80·5	4·4	5·1	9·8
	81·0	5·6	6·4	6·7
	80·0	5·3	7·8	6·9
	85·0	4·1	4·2	6·8
	84·2	3·4	5·7	6·7
	89·4	2·5	3·6	4·6
	81·9	6·0	5·7	6·6
	71·2	8·0	9·5	11·2
	78·5	4·8	7·0	9·9
	82·2	5·7	6·0	6·0
Mean	82·1	4·9	5·3	7·0
Standard Deviation ..	4·40	1·43	1·86	2·26

(b) Zone Electrophoretic Protein Fractionations in Normal Controls.—The results of the plasma protein estimations in the normal series are shown in Fig. 2 (overleaf).

Part A is the incidence chart and shows the range of values obtained for the normal group, Part B shows the pattern obtained for an average normal person, and Part C the electrophoretic curve derived from the density readings along this strip. The fractions and the percentages of each are indicated in the figure. Table II shows the ranges actually observed together with the relevant statistical calculations.

TABLE II

ZONE ELECTROPHORESIS ON SERUM OF NORMAL SUBJECTS

Estimation	Actual Range Observed (per cent. of total protein)	Mean Value (per cent. of total protein)	Sigma (per cent. of total protein)	Per cent. of Total Protein (statistical range based on mean $\pm$ 2 σ)
Albumin	61·6–78·4	68·6	4·8	59·0–78·2
Alpha-Globulin ..	2·4– 7·4	5·0	2·4	2·6– 7·4
Beta-Globulin ..	5·1–11·5	·7·5	1·8	3·9–11·1
Fibrinogen ..	7·0–15·3	10·5	2·0	6·5–14·5
Gamma-Globulin	5·1–10·0	9·4	2·5	4·4–14·4

(c) Zone Electrophoretic Protein Fractionations in Rheumatoid Arthritis.—Fig. 3 (opposite) shows the electrophoretic results for the pre-treatment control group of rheumatoid patients having normal total globulins; that is less than 2·5 g. per 100 ml. plasma. Part A is the incidence chart showing the range of values obtained. The average for each fraction was as follows: albumin 53·0 per cent.; alpha-globulin 8·5 per cent.; beta-globulin 8·5 per cent.; gamma-globulin 17·7 per cent.; fibrinogen 15·0 per cent. of the total protein. Parts B and C show the actual pattern and curve for one patient in this group.

The electrophoretic results for the total rheumatoid group are shown in Fig. 4 (overleaf). Part A is the incidence chart and shows the ranges for the individual fractions. The average for each was: albumin 54·0 per cent.; alpha-globulin 7·0 per cent.; beta-globulin 7·0 per cent.; gamma-globulin 16·0 per cent.; fibrinogen 16·0 per cent. Parts B and C show the electrophoretic pattern and curve respectively for a typical separation in this group. Parts D and E show the pattern and curve for one case with a high fibrinogen value, 26·7 per cent., and a very high gamma-globulin, 33·4 per cent.

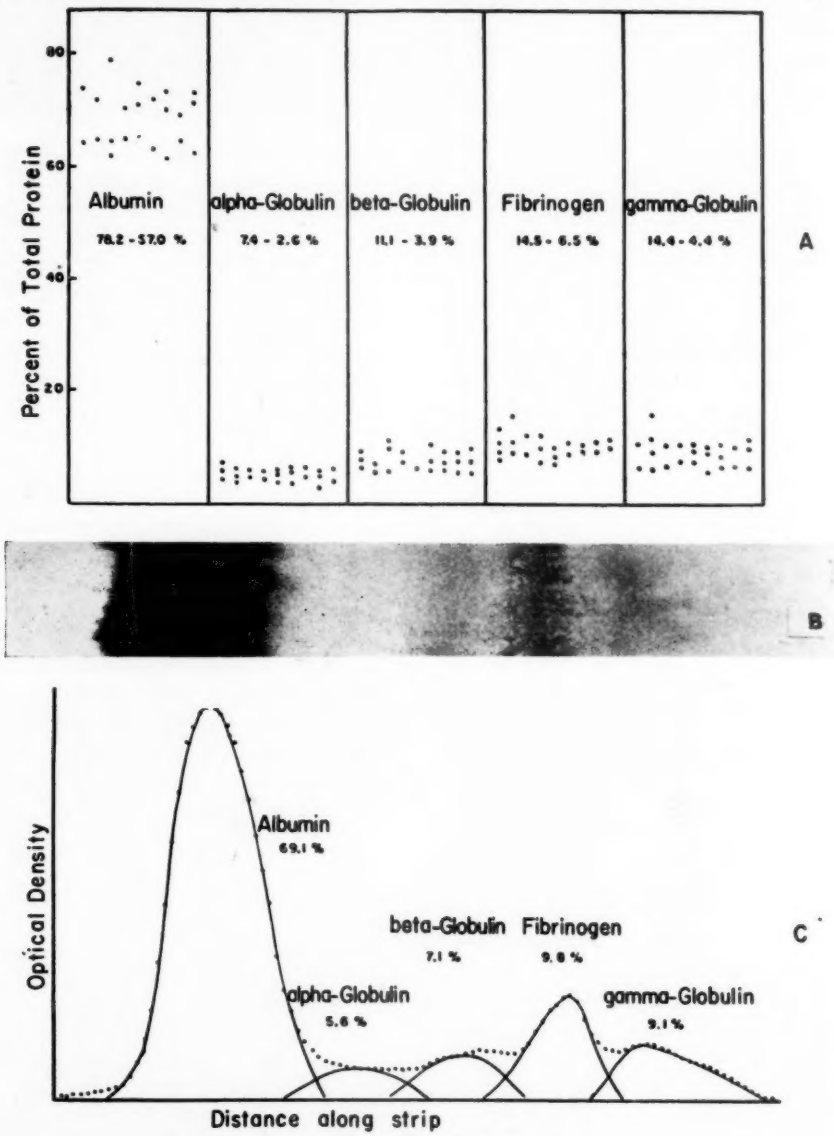


Fig. 2.—Normal series
A. Incidence of values obtained for protein fractions by zone electrophoresis.
B. Zone pattern for a typical analysis in this group.
C. Electrophoretic curve derived from B.

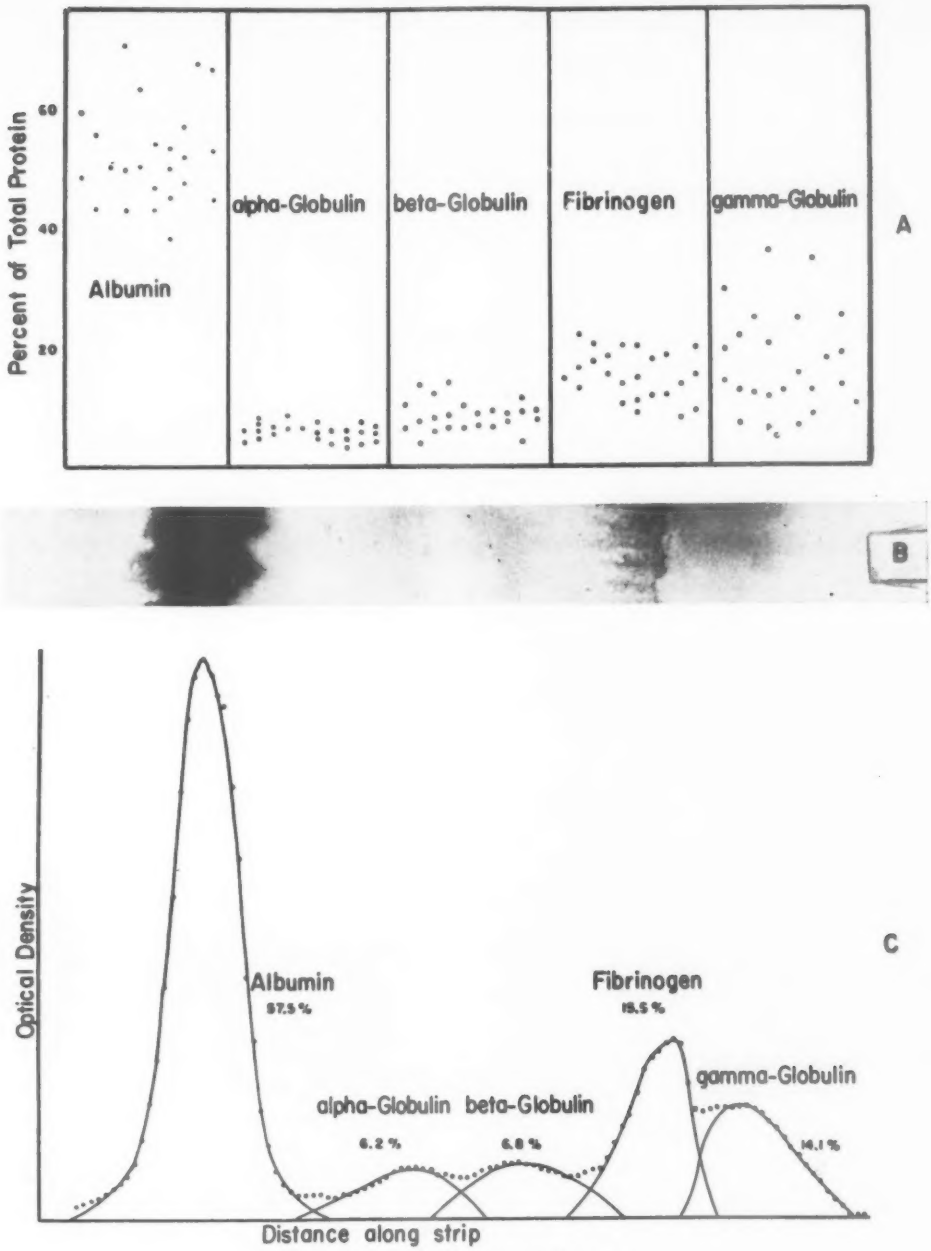
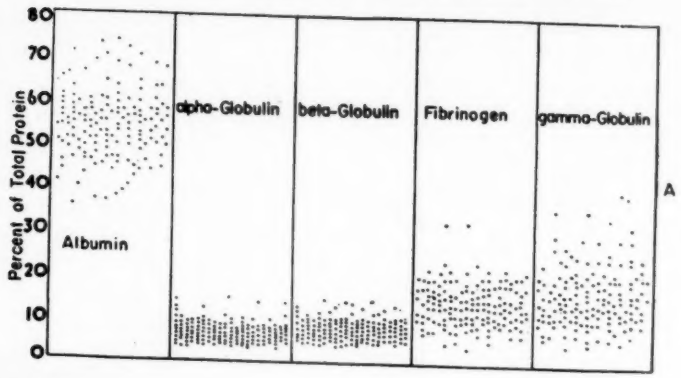
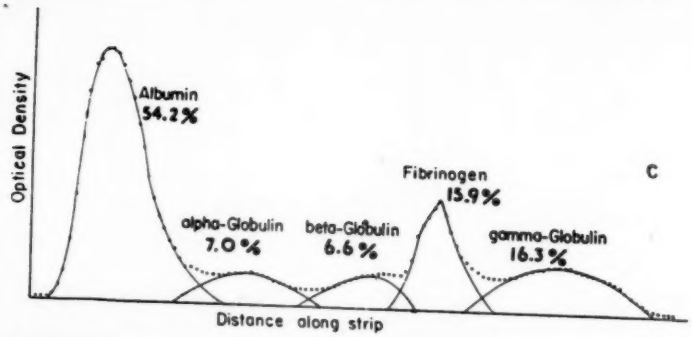


Fig. 3.—Pre-treatment control group.
A. Incidence of values obtained for protein fractions by zone electrophoresis.
B. A typical pattern for this group.
C. Electrophoretic curve derived from B.

(d) Correlation of Erythrocyte Sedimentation Rates with Fibrinogen estimated by the Two Methods.—Figs 5 and 6 (overleaf) show scattergrams of sedimentation rates and fibrinogen levels from patients with normal total globulin levels and from normal subjects. A definite linear relationship is apparent with either method of fibrinogen estimation. The statistical data is shown with the Figures. At this point it might be noted that, in the zone-electrophoretic analyses, relative fibrinogen levels only are being considered. In this study it was not attempted to obtain actual fibrinogen concentration by electrophoresis. Such a study is at present in progress and will be reported at a later date. Until such time as this is accomplished, these initial results confirm the work of the Toronto group. In addi-





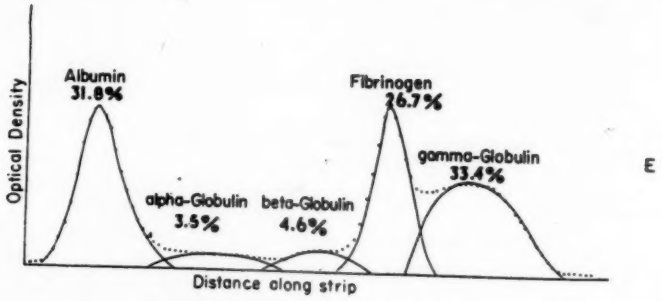


Fig. 4.—Total rheumatoid arthritic group and one extreme case.
A. Incidence chart for total rheumatoid group of 149 electrophoretic determinations.
B. Pattern of a typical separation in this group.
C. Electrophoretic curve derived from B. (Fractions and percentage of each are indicated.)
D. Pattern of an extreme case, showing very low albumin and high fibrinogen and gamma-globulin.
E. Electrophoretic curve derived from D.

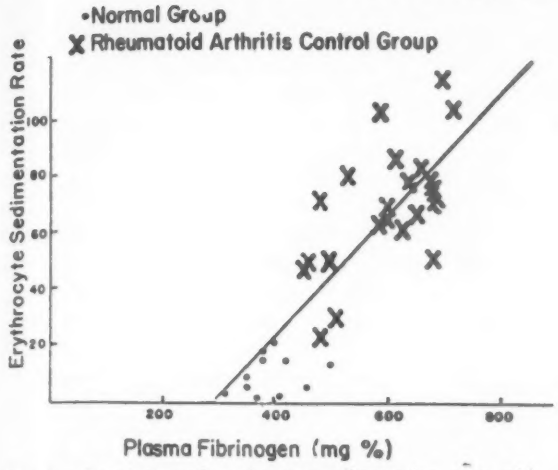


Fig. 5.—Correlation of erythrocyte sedimentation rates with fibrinogen.
Ervthrocyte sedimentation rate *v.* fibrinogen by 12·5 per cent. sodium sulphite precipitation.
Coefficient of linear correlation, $r = 0{\cdot}863$
Regression equation $E = 0{\cdot}215\ F_S - 65{\cdot}4$
where E = sedimentation rate and
F_S = fibrinogen (mg./100 ml. plasma)
$t = 5{\cdot}07$
$P < 0{\cdot}001$.

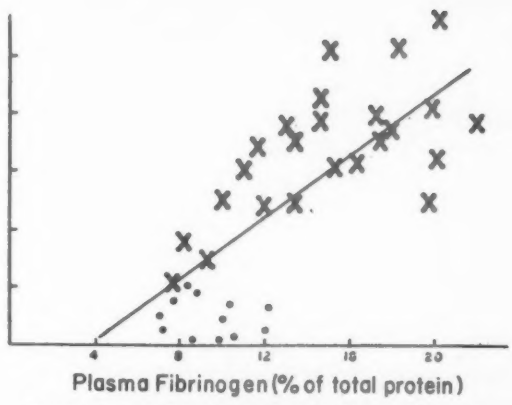


Fig. 6.—Correlation of erythrocyte sedimentation rates with fibrinogen.
Erythrocyte sedimentation rate *v.* relative fibrinogen level by zone electrophoresis.
Coefficient of linear expansion, $r = 0{\cdot}750$
Regression equation $E = 5{\cdot}64\ F_e - 25{\cdot}1$
where E = sedimentation rate
F_e = fibrinogen (per cent. of total plasma protein)
$t = 4{\cdot}50$
$P < 0{\cdot}001$.

tion, as will be discussed later, the zone-electrophoretic analysis would appear to be the less accurate of the two methods, although probably sufficiently reproducible to be of value in a general hospital laboratory, or smaller rheumatism centre.

(e) **Results of Therapy.**—As it has long been known that the fibrinogen level of the plasma and the erythrocyte sedimentation rate are indices of the activity of rheumatoid disease, these estimations were used to follow the course of patients during hospitalization with or without specific anti-rheumatic therapies.

(*i*) *No Specific Therapy.*—As was expected, only minor fluctuations in the fibrinogen levels and in the sedimentation rates occurred upon following the courses of the patients receiving no specific therapy and in the control group prior to the institution of therapy. Throughout the course of each patient study, the minor alterations in sedimentation rates closely paralleled slight changes in the fibrinogen levels.

(*ii*) *Cortisone and Combination Therapy.*—Those patients receiving cortisone showed the expected decrease in sedimentation rates and concurrent reductions in plasma fibrinogen levels during therapy with higher doses of the hormone as shown in Fig. 7. On reducing the dosage of the drug to maintenance amounts, the values of these indices tended to level off or to rise again even though the clinical features remained suppressed.

The addition of gold therapy to maintenance dosages of cortisone did not significantly alter the clinical or laboratory courses of the four patients for which this treatment was prescribed.

Small doses of phenylbutazone added to maintenance dosages of cortisone produced marked clinical improvement in three cases in this group but the fourth obtained no benefit. In the former there was a marked relief of pain and stiffness; mobility of joints increased; and a slight decrease in joint swelling occurred. However, in all cases the addition of these doses of phenylbutazone produced no alteration in the elevated sedimentation rates or fibrinogen levels.

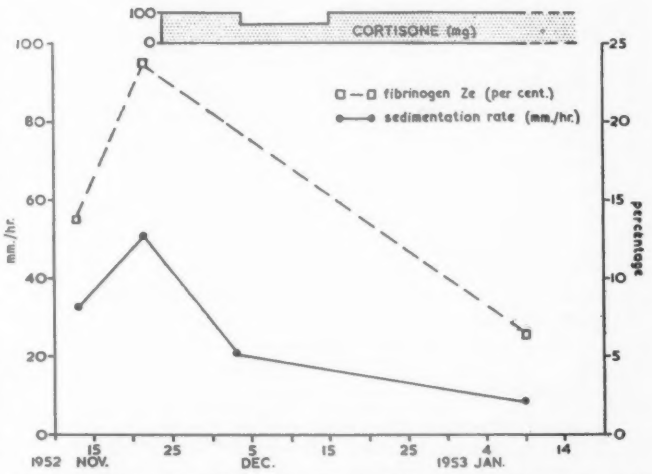


Fig. 7.—Response to cortisone in a man aged 79 of sedimentation rate and fibrinogen level (per cent. of total protein) by zone electrophoresis.

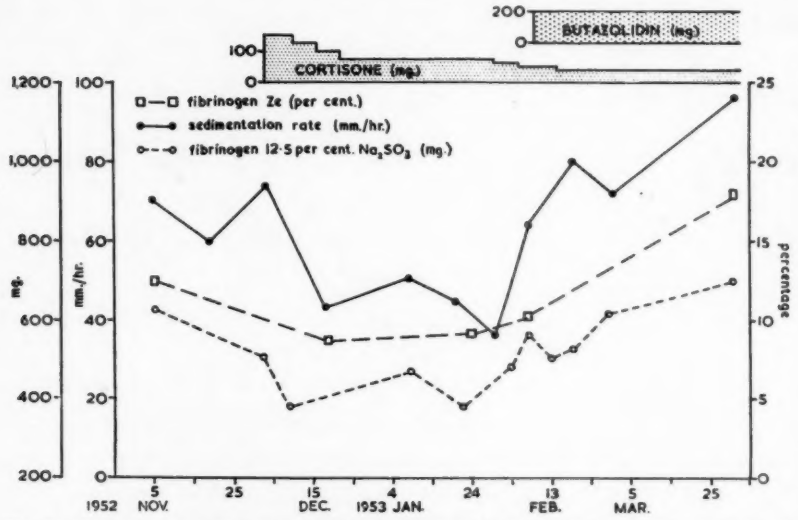


Fig. 8.—Response to cortisone with later addition of Butazolidin in a woman aged 65 of sedimentation rate, fibrinogen level by sodium sulphite precipitation, and fibrinogen level (per cent. of total protein) by zone electrophoresis.

Fig. 8 illustrates a typical case in this group. It shows a fall in all indices with satisfactory doses of cortisone and "holding" on maintenance doses of 75 mg. per day. Reducing the dosage of the hormone to 50 mg. daily or less resulted in a marked rebound which was unaffected by the doses of phenylbutazone used (200 mg. daily). This combination, however, did produce a satisfactory clinical response throughout the rest of this patient's hospital stay.

(*iii*) *Phenylbutazone.*—This drug was administered, alone, to three patients, in doses of 800 mg. per day, with gradual reduction to maintenance levels of 400 mg. daily. All received satisfactory relief of pain and increased mobility of joints. In two, joint swelling decreased. A fall in the laboratory indices, however, was seen in only one instance which is shown in Fig. 9. Again a very good correlation between the sedimentation rate and fibrinogen level is evident.

(*iv*) *Gold Therapy.*—Three patients received gold therapy in addition to the usual basic programme of balanced rest and activity, physiotherapy and remedial exercises. Moderate to marked clinical improvement occurred in all.

In one case no significant alterations appeared in either the sedimentation rates or the fibrinogen levels during the period of study. Determinations for this study were carried out on the second patient only during maintenance treatment. These revealed sedimentation rates consistently within the normal range (elevated prior to treatment) while the fibrinogen fractions of the plasma remained elevated. This seeming paradox in cases receiving gold has been well recognized.

The third patient's laboratory course was extremely erratic with many exacerbations and remissions throughout. Here, as in the first case, good correlation existed between the various indices, but no laboratory evidence of a beneficial effect from treatment was apparent.

Discussion

The zone electrophoretic technique does appear to offer possibilities as a screening method of studying protein fractionations, and the results of this study indicate that it can provide a useful means of following the course of patients with rheumatoid disease. However, the method presents a number of undesirable features which would seem to obviate its use in more detailed, exacting investigations.

Among the difficulties encountered in the zone electrophoretic technique was one termed "edge effects", by which evaporation from the edge of the glass plates tended to distort the protein pattern so that the zones were not at right angles to the axis of the paper. The effect was not a consistent one and was not readily attributed to changes in room temperature since the separation was done in a room with all openings closed. Other workers have sealed these edges by various methods; by smearing the edge with grease, or by immersing the whole assembly in water immiscible solvents. Our separations were done with a blank strip of buffer soaked paper, 1″ wide at each edge. In effect this displaced the edge effect away from the strip carrying the sample.

In addition, as has been shown in Table I, the reproducibility of results utilizing the technique

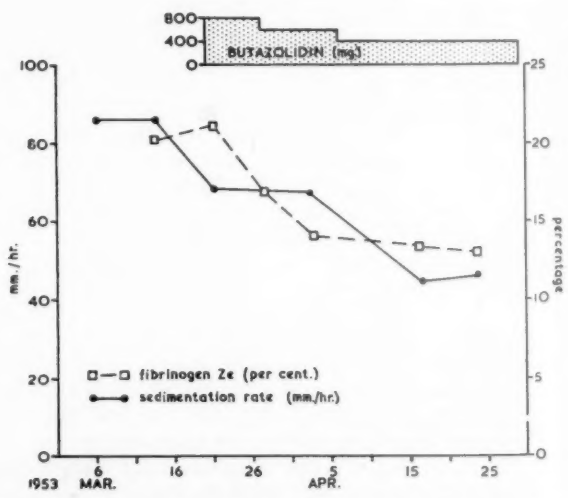


Fig. 9.—Response to Butazolidin in a woman aged 53 of sedimentation rate and fibrinogen level (per cent. of total protein) by zone electrophoresis.

described leaves something to be desired. Also the percentage levels for fibrinogen (Table II) for normal controls are found to be consistently high as compared with other methods.

The problem here would appear to involve mainly difficulties in deriving the points of separation between the various fractions, particularly the fibrinogen and gamma-globulin. This became evident both during the scanning of the coloured strips, and during the plotting and calculation procedures. In an attempt to obtain better separation, other workers, such as Kay (1954), have employed smaller currents of longer duration and have utilized different dyes. These modifications would appear to be very advantageous for analyses of serum, but, in the case of plasma, difficulties still exist in the separation of the two fractions noted previously. This is because of the slow and almost equal movements of these two components during electrophoresis, which almost always result in some degree of overlapping of the fibrinogen and gamma-globulin fractions (Figs 2, 3, and 4).

Again, it has been observed that the fibrinogen, particularly when increased in amount, tends to "gel" resulting in irregular, streaky distribution on the filter paper of this component and the gamma-globulin as well (Fig. 4D). This phenomenon was greatly increased when stored specimens were analysed, as was noted earlier, and it was minimized by the use of absolutely fresh plasma samples.

For these reasons, and until they can be overcome, this technique as applied to plasma protein fractionations would seem to be inferior to the older methods of study.

On the other hand, the apparatus and procedures are relatively simple, and the saving of technical time, as compared with other methods, is considerable. These factors, together with its demonstrated clinical applicability, indicate that the zone electrophoresis technique of serum or plasma fractionations can be utilized in the laboratories of smaller general hospitals or rheumatism centres.

Summary

(1) A relatively simple method of estimating the five major components of the plasma protein is described, together with the apparatus used.

(2) By this method, in rheumatoid arthritis and ankylosing spondylitis, a moderate to marked rise is found in the relative fibrinogen and gamma-globulin levels, while the plasma albumin tends to be correspondingly reduced. No significant alterations in alpha- and beta-globulins are apparent.

(3) The results of the study relating sedimentation rate estimations to plasma fibrinogen levels in rheumatoid disease again demonstrate, as shown by Fletcher and others (1952), the linear correlation between these factors. This correlation is not as impressive with fibrinogen percentage levels obtained by zone electrophoresis as with the estimations obtained by precipitation with sodium sulphite. However, the former is statistically significant and indicates that the technique used is suitable for general clinical use, particularly in patients with rheumatoid disease.

(4) The progress of various patients has been followed during various forms of therapy, and typical graphs are presented utilizing the sedimentation rate and plasma fibrinogen levels as indices of the activity of rheumatoid disease.

(5) Some of the problems and undesirable features of the technique are discussed.

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Étude des protéines sanguines par zones d'électrophorèse dans l'arthrite rhumatismale et dans la spondylarthrite ankylosante

RÉSUMÉ

(1) On décrit une méthode relativement simple, ainsi que l'appareil, pour déterminer les cinq composants principaux des protéines du plasma.

(2) Par cette méthode on trouve que dans l'arthrite rhumatismale et dans la spondylarthrite ankylosante il y a une augmentation modérée ou prononcée des taux relatifs du fibrinogène et de la gamma-globuline tandis que le taux de l'albumine du plasma tend à diminuer en proportion. On n'observe pas d'altérations significatives de la alpha- ni de la beta-globuline.

(3) La corrélation de la vitesse de la sédimentation globulaire et du taux du fibrinogène sanguin dans la maladie rhumatismale confirme les résultats de Fletcher et coll. (1952) montrant l'existence d'un rapport direct entre ces deux facteurs. Ce rapport n'est pas aussi impressionnant avec les chiffres du fibrinogène obtenus par la méthode électrophorétique qu'avec ceux qu'on obtient par la précipitation au sulfate de soude, mais il

demeure toujours significatif du point de vue statistique. Le procédé décrit se prête donc à l'application clinique générale, surtout chez les rhumatisants.

(4) On a surveillé des malades au décours de différentes formes de traitement et on présente ici des courbes typiques, construites à l'aide des chiffres de la vitesse de la sédimentation globulaire et du fibrinogène sanguin comme indices d'activité de la maladie rhumatismale.

(5) On discute quelques problèmes et traits indésirables du procédé.

Estudio de las proteinas sanguíneas por zonas de electroforesis en la artritis reumatoide y en la espondilartritis anquilosante

SUMARIO

(1) Se describe un método relativamente simple, con el aparato empleado, para determinar los cinco componentes principales de las proteinas del plasma.

(2) Con este método se ve que en la artritis reumatoide y en la espondilartritis anquilosante hay aumentación moderada o pronunciada de las cifras relativas del fibrinógeno y de la gama-globulina mientras que la cifra de la albumina del plasma tiende a bajar en proporción. No se observan alteraciones significativas en la alfa- ni en la beta-globulina.

(3) La correlación de la velocidad de la sedimentación eritrocitaria con la cifra del fibrinógeno sanguíneo en la enfermedad reumatoide confirma los resultados de Fletcher y otros (1952) que hay relación directa entre estos factores. Esta relación no es tan impresionante con las cifras de fibrinógeno obtenidas por el método electroforético que con las que se obtiene por la precipitación con el sulfato de sodio, pero queda significativa estadisticamente. El método descrito conviene pués para el empleo general clìnico en particular en los reumáticos.

(4) Enfermos sometidos a varias formas de tratamiento fueron seguidos, presentándose aquí las curvas tìpicas, construidas con la ayuda de la velocidad de la sedimentación eritrocitaria y de las cifras del fibrinógeno sanguíneo como índices de actividad de la enfermedad reumática.

(5) Se discute algunos problemas y rasgos indeseables del procedimiento.

COMPLEMENTARY ACTIVITY OF THE BLOOD IN RHEUMATISM AND CERTAIN ALLIED DISORDERS

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In the study of rheumatic fever there has been, as Fischel, Pauli, and Lesh (1949) remark, "disagreement and confusion as to the level of serum complement". Though Weil and Buchholz (1932) and Coburn (1936) have reported a low complement of the serum, rising to normal with the subsidence of activity, both these authors and Hadjopoulos and Burbank (1928) noted high values during the early period of rheumatic activity and low values later. It was formerly thought (Kellett, 1936) that, in certain cases, the onset of the disease was associated with a low level of complement in the blood, but, whereas in acute nephritis this fall seemed to be related to the onset of acute glomerulonephritis, no such clear relationship was discerned in the rheumatic cases. Recently, however, the opportunity has occurred of repeating this work on a larger scale, making use of methods better calculated to give accurate results, and it is with these that this paper is concerned.

Method

Burroughs Wellcome sheep cells were used throughout and sensitized with the Burroughs Wellcome haemolytic serum (glycerinated) for sheep corpuscles. Instead of ordinary saline, Brook's modified saline was used; this was made up as follows:

NaCl 170 g.
KH_2PO_4 2·78 g.
NA_2HPO_4 11·3 g. (equivalent to NA_212H_2O 28·5 g.)
Distilled water to 1,000 ml.

This was kept as a stock solution and, before use, was diluted 1/20 with distilled water.

Exactly 5 ml. sheep blood cells were placed in a centrifuge tube and washed three times in the modified saline solution and made up to the original quantity. These were added to 45 ml. modified saline, giving a 1/10 dilution of washed cells. 0·2 ml. haemolytic serum was added to 50 ml. modified saline, and, in this form, was mixed with the red blood cell suspension. The mixture was allowed to stand at room temperature for 15 minutes (immune body being present in slight excess). Each serum to be tested was drawn off a sample of blood, which had been allowed to clot and had been stored overnight in a refrigerator, and diluted 1/50 in the modified saline. The test was set up as shown in the Table.

The tubes were placed in a water bath at 37° C. for 45 minutes, and centrifuged; the amount of haemolysis in the supernatant fluid was determined on an E.E.L. colorimeter, and the result expressed in terms of percentage of total haemolysis.

In Figs 1 to 4 have been plotted the readings obtained by this method in certain different types of patients admitted to the wards during the 2 years when this investigation was proceeding. In each instance, where more than two estimations were carried out, the highest and lowest readings obtained have been recorded.

Results

It is apparent that, whereas the level of complementary activity varied within a relatively narrow range in a group of people complaining of stomach pain, regarded as a control group, this range of activity was far greater in cases of rheumatoid arthritis and rheumatism, and was, indeed, almost comparable to that encountered in acute nephritis; furthermore, though in certain instances it would

TABLE
METHOD OF SETTING UP TEST

Tubes	1	2	3	4	5	6	7	8	9	10	11
Diluted human serum (ml.)	5·0	4·5	4·0	3·5	3·0	2·5	2·0	1·5	1·0	0·5	0
Modified saline (ml.)	0·5	1·0	1·5	2·0	2·5	3·0	3·5	4·0	4·5	5·0	5·5
Sensitized cells (ml.)	2·0	2·0	2·0	2·0	2·0	2·0	2·0	2·0	2·0	2·0	2·0

seem as if for a time complementary activity was enhanced, in a greater number of examples of abnormality, the activity was reduced. In the majority of cases encountered during this period, however, the disease had been present for a number of years, and, in these, the complementary activity of the blood seemed to rest within the normal range and did not vary with the blood sedimentation readings.

From these curves, moreover, it is possible in each instance to determine the amount of serum required to bring about a 50 per cent. haemolysis in the system employed. If this be considered a unit, then it may be convenient to express the activity of the serum in terms of the number of the units contained per ml. Such a simplification would seem legitimate, provided it be clearly understood that this measure refers, not to an absolute quantity but rather to an activity under certain reproducible conditions. Figs 1 to 4 may then be said to show that, whereas the sera obtained in patients suffering from gastric disorders contains 20 to 50 units/ml., those from cases of rheumatoid arthritis contained from 0 to 67 units/ml., from rheumatic fever from 12 to 62 units/ml., and from nephritis from 0 to 50 units/ml.

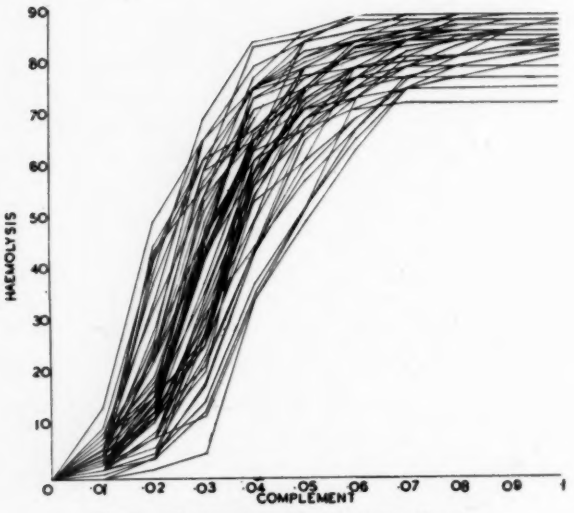


Fig. 1.—Changes in activity in gastric disorders.

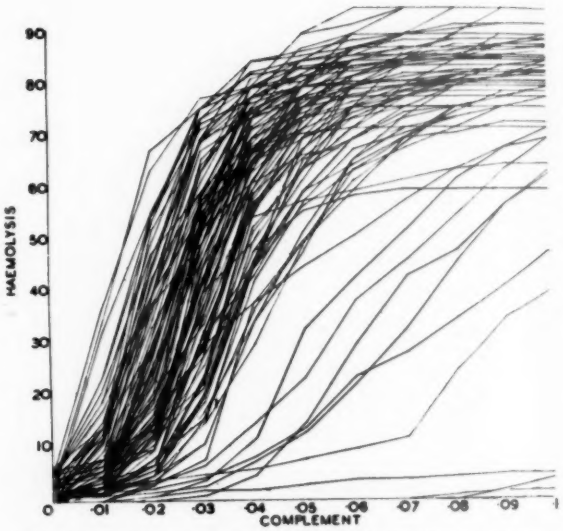


Fig. 2.—Changes in activity in rheumatoid arthritis, spondylitis, and lupus erythematosus.

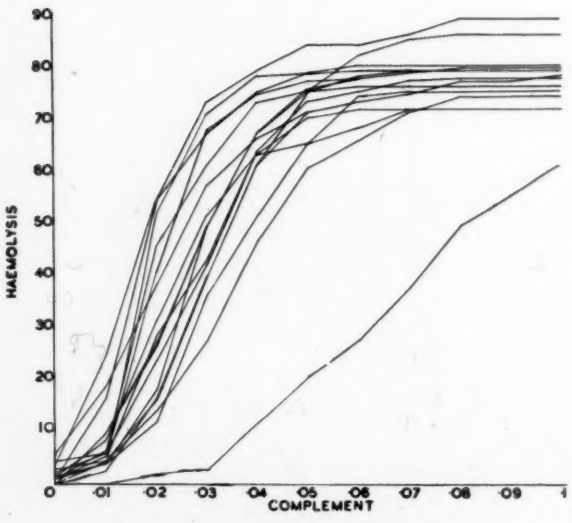


Fig. 3.—Changes in activity in rheumatic fever.

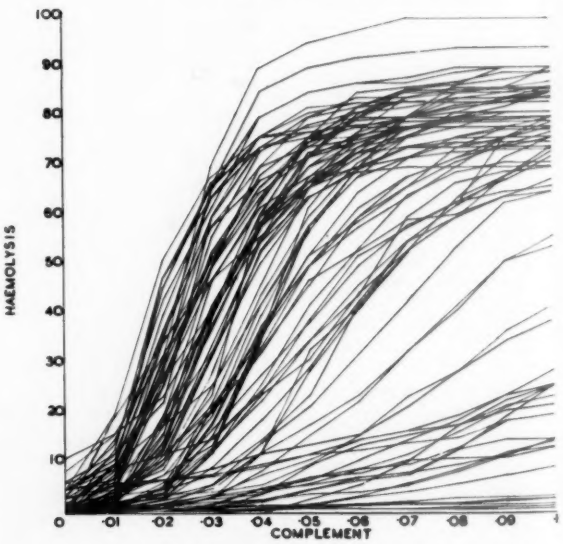
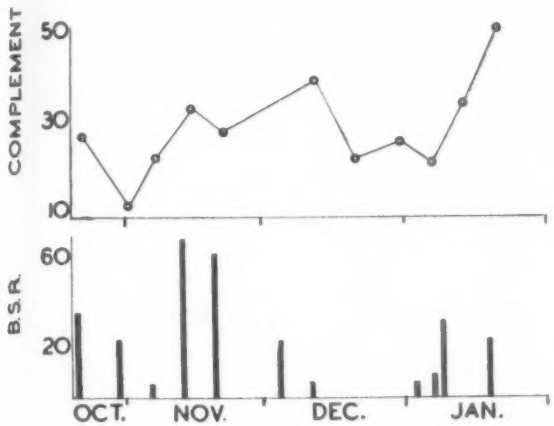


Fig. 4.—Changes in activity in nephritis.

Rheumatic Fever.—Relatively few cases were encountered during the 2 years under review.

Fig. 5 summarizes the changes in Case 1, a girl aged 16, who had had a previous attack at the age of 6 but had remained free from further attacks until 3 weeks before admission. She then had severe tonsillitis, followed a fortnight later by pain and redness of the right knee; the majority of the other joints of her body were subsequently involved, but responded, within 24 hours of admission on October 20, 1951, to 20 gr. sodium salicylate three times a day. She was maintained on this for the next 2 months. During this time she was symptom free but developed signs of aortic incompetence, which have persisted up till the present.



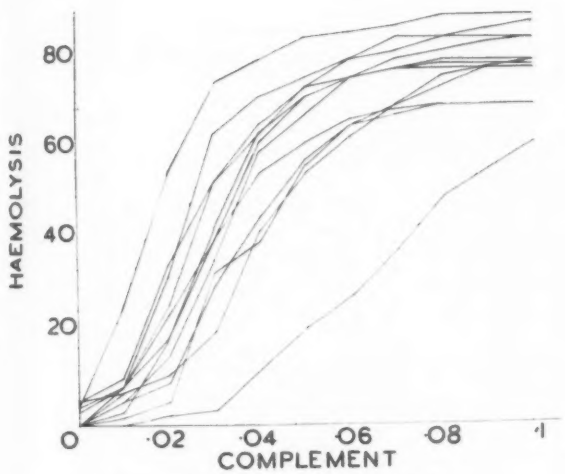


Fig. 5.—Case 1, girl aged 16, rheumatic fever.

Case 2 (Fig. 6), that of a boy aged 16, was under review for 3 months. This was his first attack; it followed a week after a severe sore throat, and was in this instance treated by a course of cortisone, which promptly relieved the symptoms but which, on cessation, was immediately followed by a relapse, so that he was given another course. He too developed aortic incompetence, and, 5 weeks after his last course was completed, profound mental changes, which have persisted.

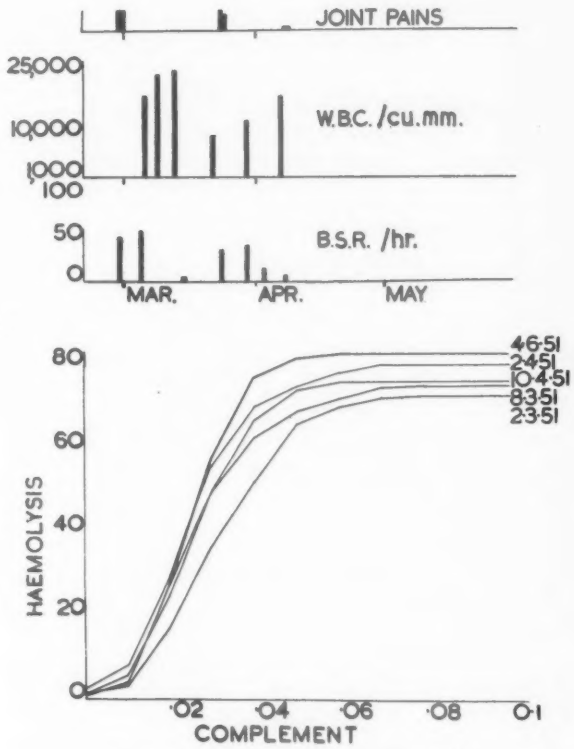


Fig. 6.—Case 2, boy aged 16, rheumatic fever.

In Case 1 the changes in complementary activity were slight and seemed to bear no relation to those in the blood sedimentation rate; in Case 2 there were no such changes. In both instances convalescence was marked by high levels.

Rheumatoid Arthritis.—Several cases were seen for a short time only, for the purpose of determining whether or not they were likely to benefit from a course of cortisone, so that though 79 cases were tested for complementary activity, 44 were only tested once and nineteen twice, the remainder being tested on three or many more occasions. In the first group (44 readings), 36 lay between 20 and 40 units/ml. with one below and seven above. In the second group (38 readings), 31 lay between 20 and 40 units/ml., with one below and six above. It would seem that isolated readings in the majority of cases of rheumatoid arthritis would lead to results well within the normal range.

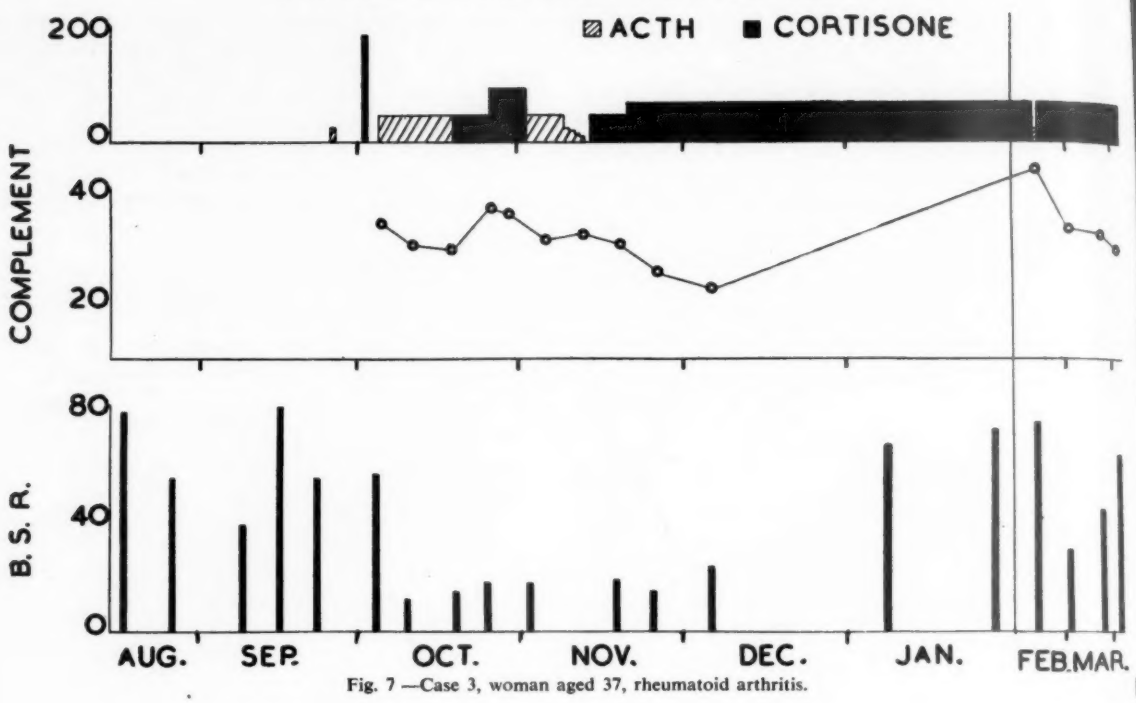


Fig. 7 —Case 3, woman aged 37, rheumatoid arthritis.

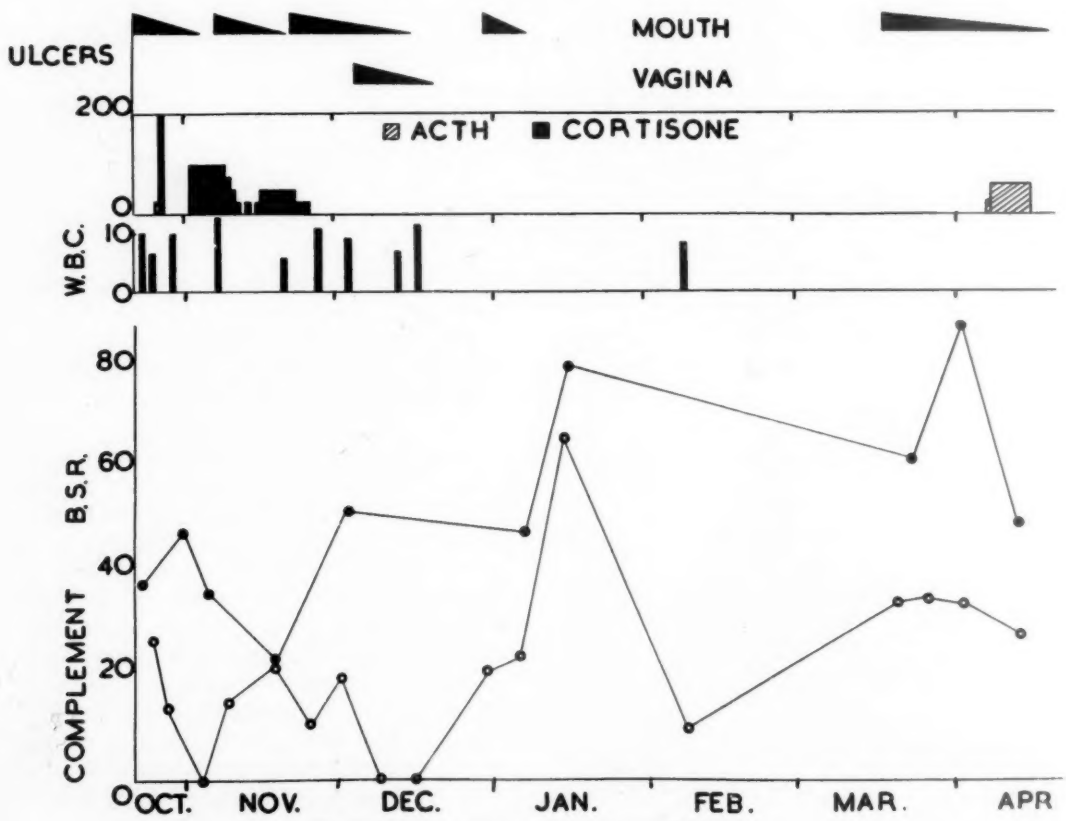


Fig. 8.—Case 4, woman aged 29, rheumatoid arthritis.

Fig. 7 (opposite) summarizes the main changes seen in Case 3, a woman aged 37, with severe rheumatoid arthritis which had been progressive for the past 6 years, until all the joints had become involved. Though there had been a temporary response to courses of gold injections, radiant heat, and spa therapy, this patient had become almost crippled. She responded fairly well to cortisone and ACTH and was one of the few to be kept on permanent maintenance doses of these substances.

Fig. 8 (opposite) summarizes the findings in Case 4, a woman aged 29, with rheumatoid arthritis of 8 years' duration, which involved first the ankles and knees, and subsequently spread to the elbows. She had had psoriasis since childhood, and, while in hospital, developed multiple ulcers of the mouth and vagina, which were very resistant to treatment. It was thought possible that this might be a case of lupus erythematosus, but typical cells were not detected. There was no leukopenia and the Wassermann reaction and gonococcal complement-fixation test were negative. After 3 years she is in fairly good general condition, though she is gradually becoming more crippled by arthritis.

Lupus Erythematosus.—Only two proven cases were investigated during this period. In both the disease was associated with a marked fall in the complementary activity of the blood.

Fig. 9 summarizes the findings in Case 5, a woman aged 22, who was kept under observation for a number of years. She was first seen in September, 1946, when she appeared to have rheumatoid arthritis, which responded well to a course of gold treatment; 4 years later she was admitted with a pericardial effusion and was considered to be suffering from pericarditis, associated with active rheumatoid arthritis. She was re-admitted 3 months later, having had two further

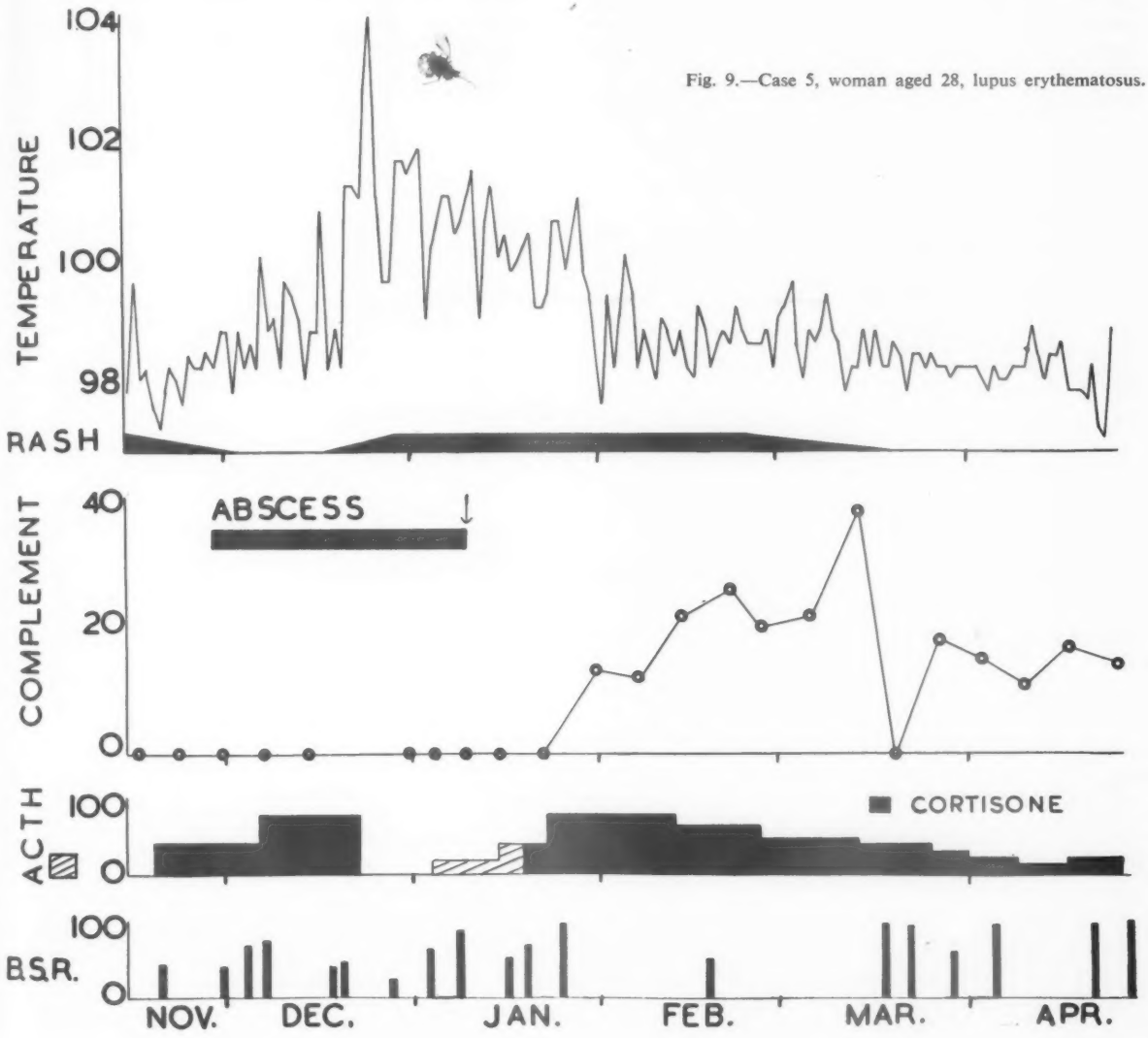


Fig. 9.—Case 5, woman aged 28, lupus erythematosus.

attacks of what appeared to be a diffuse rheumatic process associated with a skin rash, and lupus erythematosus involving her eyebrows, cheeks, and nose. Liver function tests and a skin biopsy were normal. A year later she was admitted with an exacerbation of her general condition and a diagnosis of disseminated lupus erythematosus established. She responded, to begin with, to cortisone, but her condition deteriorated and she died at the age of 28 on September 9, 1952. The most marked changes found at autopsy were in the kidneys, where there was a severe degree of glomerular damage, mostly in the form of fibrinoid necrosis in focal masses, sometimes involving nearly all the glomerulus.

Case 6, a woman aged 29, was seen by the author on only two occasions (Fig. 10). Her illness had begun with a swelling of the fingers and wrists, 4 months before admission, and had subsided after a period of rest, but had recurred. To begin with she again appeared to do fairly well with rest, but after the second month she developed a continuous fever, her spleen became palpable, and, 3 months after admission, extensive painful ulcers occurred in the mucous membrane of the mouth and palate. She did not respond either to penicillin, chloromycetin, or streptomycin. In addition she had recurrent rashes, with a loud systolic murmur, and signs of pleural involvement. She ultimately died, 7 months after admission, on March 26, 1952. A diagnosis of sub-acute lupus erythematosus was confirmed at autopsy.

In Cases 5 and 6 the changes in the complementary activity of the blood are more marked than in those previously recorded, and it would be tempting to believe that the extent of the fall was in some way linked up with the severity of the disease process.

Spondylitis.—The following case, however, emphasizes the difficulties that arise once an attempt is made to establish such a correlation.

Fig. 11 summarizes the findings in Case 7, a young man aged 32, who had been perfectly well until 3 months before admission, when he had had an influenza-like illness, which kept him in bed for 3 weeks. Shortly after this, he developed such acute pain in the muscles of the back that he was unable to move and had to lie flat in bed. At the age of 7 he had had chorea but had had no rheumatism since then. His blood sedimentation rate on admission was 95 mm./hr. *X* rays of his spine and an electrocardiogram were normal. The blood picture and liver function tests were within normal limits. To begin

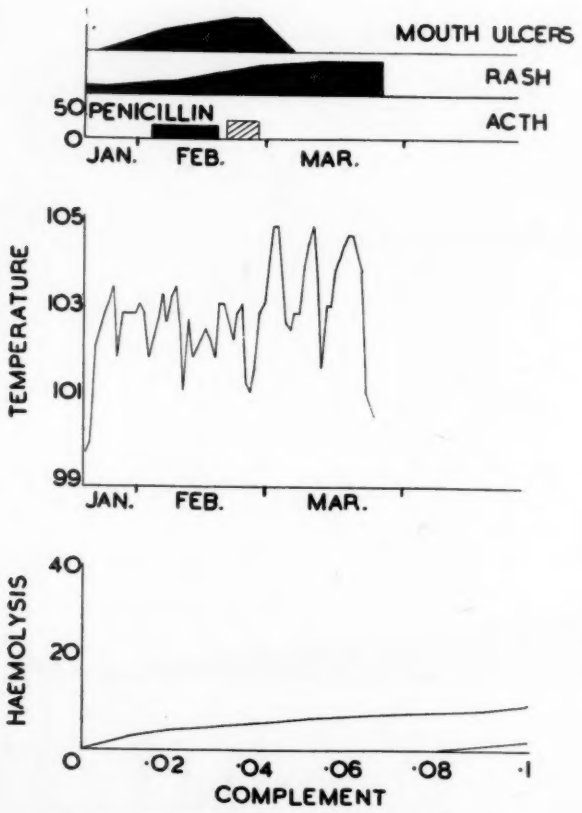


Fig. 10.—Case 6, woman aged 29, lupus erythematosus.

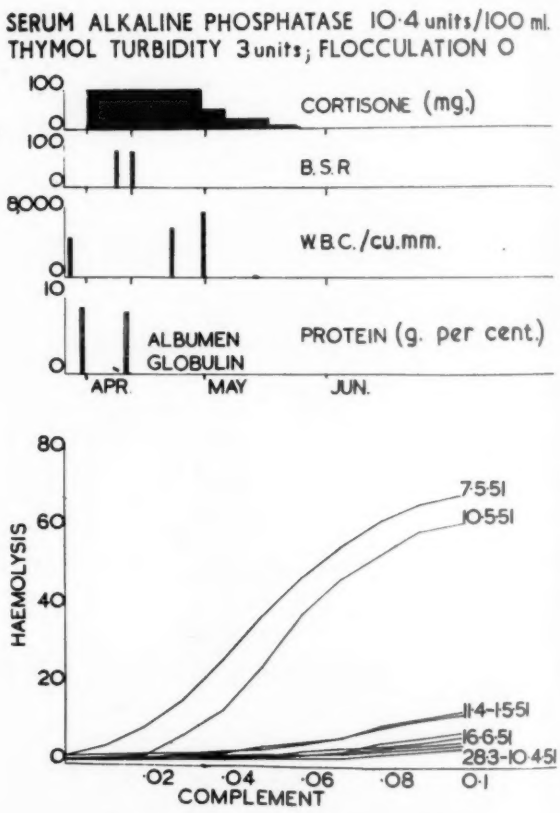


Fig. 11.—Case 7, man aged 32, spondylitis.

with, he improved on salicylates but this improvement was of short duration, and he was, therefore, placed on cortisone, which resulted in a very dramatic change. He was able to sit up in bed, with a full range of movements, and felt so well that he ultimately discharged himself and returned to work. He managed fairly well for about a year, when his pains returned. He again became so bad that he had to give up work 4 months ago and was sent to hospital to see an orthopaedic surgeon. His blood sedimentation rate was found to be 85 mm./hr, and a diagnosis of spondylitis was again made, although the radiologist reported no obvious changes in his spine. He has had a course of radiotherapy, but his back is still stiff and he is at present having physiotherapy.

Discussion

Waaler (1937) encountered serum from a case of rheumatoid arthritis which inhibited the haemolysis of sheep red cells and also caused marked agglutination of the same cells in the presence of a small amount of haemolytic amboceptor. While haemolytic amboceptor was used in slight excess throughout our experiments, and we did not, so far as we are aware, encounter this phenomenon of agglutination, it might well be urged, in a case such as this, that the initial fall in complementary activity was due either to the appearance of anti-complementary substances in such excess as to mask any subsequent recovery, or to a reaction such as that described by Waaler.

The simple experiment recorded in Fig. 12 would, however, suggest that this is not so. A sample of the Serum A, taken on the first occasion the patient was seen and found to be without complementary activity, was diluted 1/25 instead of the routine 1/50 and added to an equal quantity of a similar dilution of Serum B from another patient in whom the complementary activity was depressed to within the lower limits of normality. Having been allowed to stand for 30 minutes at room temperature, the activity of the mixture containing each serum in the routine dilution of 1/50 was assessed by the method employed throughout this work (c). As in similar experiments carried out in cases of nephritis, the complementary activity of the mixture was the greater, implying the absence of anti-complementary substance in excess or of any effect similar to that described by Waaler.

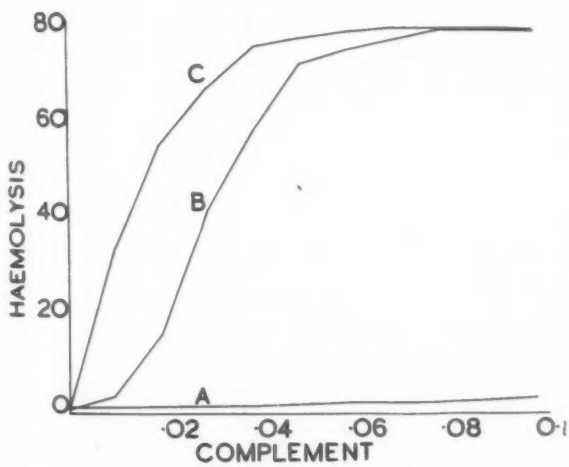


Fig. 12.—Experiment assessing two sera (A and B), and a mixture of the two (C).

Nevertheless, there does appear to be an inverse relationship between our findings and those of workers carrying out the test based on this effect. Alexander and de Forest (1954) found it to be negative in just those conditions in which we found complement most diminished (namely: lupus erythematosus, arthritis with psoriasis, and ankylosing spondylitis), and positive in the majority of cases of rheumatoid arthritis, in which we found little change in the complementary activity of the blood. It would seem, therefore, that, if there is a relationship between these agglutinins of the blood and the diminished complementary activity, it is one which could perhaps be best explained on the assumption that both the agglutinins and complement had become used up in some form of reaction, and it may well be that further study of these changes along such lines, might prove of value.

The work of these 2 years has, unfortunately, done little to dispel the disagreement and confusion referred to at the beginning of this paper. The method employed may tend to make a rise in complementary activity of the blood less obvious than a fall, but, so far as our findings are concerned, this fall would appear to be a more striking phenomenon than the rise referred to by Fischell, Pauli, and Lesh (1949), and it may well prove to be a significant finding in cases of lupus erythematosus. Such changes can hardly be devoid of meaning, and it would seem that further study of this phenomenon may well be worth while.

Summary

There is at present no general agreement as to the changes in the complementary activity of the blood that may occur in rheumatoid arthritis and certain apparently allied conditions, such as ankylosing spondylitis, arthritis with psoriasis, and lupus erythematosus. Rather marked variations of activity are, however, encountered, particularly in the last three conditions, in which activity may be greatly impaired, and it is, perhaps, significant that Waaler's reaction, in a recent series by Alexander and De Forest, proved in these to be negative.

It is a pleasure to have this opportunity of thanking Miss G. Partington and Miss A. Stickland, my technical assistants, who carried out the complementary estimations; my colleagues, for their ready co-operation; and the Newcastle-upon-Tyne Regional Hospital Board for the research grant which made this work possible.

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Activité du complément sanguin dans le rhumatisme et dans certaines affections apparentées

RÉSUMÉ

A présent il n'y a pas d'accord général sur les variations de l'activité du complément sanguin pouvant survenir dans l'arthrite rhumatismale et dans certaines affections apparentées, telles que la spondylarthrite ankylosante, l'arthrite psoriasique et le lupus érythémateux. Des variations sssez prononcées, cependant, se rencontrent, surtout dans les trois dernières affections, dans lesquelles cette activité peut être considérablement affaiblie, et il semble significatif que, selon les expériences récentes d'Alexander et de De Forest, la réaction de Waaler y soit négative.

Actividad del complemento sanguíneo en el reumatismo y en algunos disturbios aliados

SUMARIO

No existe al presente acuerdo general respecto a variaciones de la actividad del complemento sanguíneo susceptibles de producírse en la artritis reumatoide y en algunas afecciones aliadas, como la espondilartritis anquilosante, la artritis con soriasis y el lupus eritematoso. Encuéntranse, sin embargo, variaciones bastante pronunciadas, particularmente en las tres últimas afecciones en las cuales puede haber considerable disminución de esta actividad; parece significativo que, según la experiencia reciente de Alexander y de De Forest, la reacción de Waaler fuera negativa en estos disturbios.

HISTOLOGICAL STUDIES OF PELVO-SPONDYLITIS OSSIFICANS (ANKYLOSING SPONDYLITIS) CORRELATED WITH CLINICAL AND RADIOLOGICAL FINDINGS

BY

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Clinical and radiological studies (Romanus and Ydén, 1952a,b; Romanus, 1953) offer a new and more coherent concept of ankylosing spondylitis, and help to explain certain characteristic features, such as its progression from the sacro-iliac joints up the spine and into the pelvis, with combined pelvic, spinal, and peripheral symptoms, and its predominance in male patients. These studies have suggested the designation "pelvo-spondylitis ossificans". The results of nineteen biopsies of specimens from different skeletal regions, and an examination of one autopsy case are reported below. This series shows the histological appearance of the disease at different stages, and assists in the interpretation of the radiological changes.

Until the last few years our knowledge of the changes in pelvo-spondylitis ossificans has been based on some fifty autopsy reports, most of them in an advanced stage of disease and incompletely described. Recently reviews have been published by Collins (1949), Goslings (1951), Van Swaay (1950), and Aufdermaur (1953). There are also histological descriptions of individual specimens from peripheral joints, mostly taken from chronic cases in connection with arthroplasty. Cruickshank (1951) published an excellent description of three autopsy cases, and nine biopsies of specimens from peripheral joints in a more acute phase.

Most authors now agree that, in advanced cases, the disease is clearly differentiated clinically and radiologically. Its central feature, in addition to the initial sacro-iliac arthritis, is taken to be an ankylosing arthritis in the apophyseal joints of the spine with secondary ossification.

The views set forth below are based on the clinical and radiological examination of some 130 cases of pelvo-spondylitis (Romanus and Ydén, 1954). Our findings in frequent follow-up *x*-ray examinations of pelvo-spondylitis cases do not correspond with the current view that the vertebrae are normal except for osteoporosis, but show that pelvo-spondylitis is a true spondylitis with involvement of all the elements of the spine. Similar changes occur also in the pelvis, in addition to the sacro-iliac joints, and in certain other sites such as the sternal synchondrosis, the joints of the clavicle, and the calcaneus.

Those who have examined large series of cases of pelvo-spondylitis now agree that bilateral arthritis in the sacro-iliac joints is the earliest demonstrable radiological change. These changes in these joints have been exhaustively studied and described; they begin with inflammatory decalcification, resorption leading to lytic defects, destruction, ossification, proliferation to synosteosis, and reconstruction.

As regards the spinal changes, attention has been concentrated on the apophyseal joints and "ligamentous ossification". Detailed studies of a large number of cases, which were examined radiologically at frequent intervals from the onset of the disease until the classical ossification had developed, showed this ossification to be secondary to a destructive phase, to which attention had not previously been drawn. In the ventral portions of the vertebrae there is often a true spondylitic destruction, which may wear away the vertebral body margins. Thus the anterior contour of the vertebra, normally concave, becomes straight or even convex—the so-called squaring of the vertebral body. Secondary ossification may sometimes lead to the body of the vertebra regaining its original shape by the formation of new bone. The so-called syndesmophytes localized at the lateral part of the vertebral body are preceded by a similar, but superficial, destruction of the cortical layer of the body. In several cases similar changes, though not so marked, could be demonstrated on transverse and spinous processes.

In all these skeletal localizations the same phases can be distinguished as in the sacro-iliac joints: an initial phase with inflammatory decalcification, bone resorption and destruction, and possibly reactive sclerosis in adjacent tissues, and a secondary reparative phase with proliferation, ossification, and reconstruction. The two types of change may be present concurrently in, for instance, different parts of the sacro-iliac joints, on the surface of the ischial tuberosity, and on the anterior surface of the vertebral body. The intervertebral disks are not normal in pelvo-spondylitis; in several cases there was evidence of a progressive narrowing of one or more lumbar intervertebral spaces. Examination

of the lower lumbar disks (in thirty cases) by discography showed a relatively common occurrence of disk rupture, and in some cases disk prolapse. Furthermore, atypical disk degeneration was seen, with the formation of cavities in the anterior portion. This may be the expression of special pelvo-spondylitic changes (similar changes are found in autopsy pictures, *e.g.*, Forestier and others (1951).

This radiological similarity in the appearance and evolution of changes in different skeletal localizations led us to study the histopathology of the first destructive phase by biopsies of specimens from relatively accessible skeletal regions, such as the spinous process with adjacent soft tissue.

First we selected patients showing tenderness over the prominent part of the iliac crest, and over spinous processes which had become prominent as a result of back deformity and atrophy of the deep muscles of the back. Later, patients showing clinical fixation of the spine who could not be adversely affected by the operation were chosen.

As the majority of patients showed subjective improvement after the operation, we finally selected a few relatively early cases with moderate spinal symptoms. In pre-operative *x*-ray examination slight osteolytic changes had been suspected on the tips of the spinous processes in some cases, but no definite changes were found, with the exception of small bone deposits. The rest of the biopsy specimens were taken in operations performed on the grounds of the patients' subjective symptoms.

Material

A. Twelve biopsy specimens from the spinous processes with adjacent soft tissue.
B. Two biopsy specimens from the iliac crest with connective tissue from the layer against the periosteum.
C. Two biopsy specimens: (*i*) hip-joint; (*ii*) acromio-clavicular joint.
D. Two biopsy specimens from the sternal synchondrosis.
E. One biopsy specimen from the intervertebral disk L5/S1.
F. Spine from an autopsy case.
G. Control series for A: spinous processes with adjacent soft tissue from twelve autopsy cases lacking any apparent joint or skeletal disease.

Method

Cultures were made of finely ground pieces of tissue from A, B, C*ii*, and D, with negative results. There was certainly a sparse growth of *Staphylococcus albus* in four cases, but this was thought to be due to contamination.

The majority of the specimens were *x*-rayed after resection and fixed in formalin. The bone tissue was then decalcified in 5 per cent. trichloracetic acid, the material was embedded, and sections were prepared and stained according to normal histological methods. The specimens from the spinous processes were divided in a saggital direction, each half being sectioned at different levels.

Results

A and B. Biopsies from Spinous Processes and Iliac Crests

Radiological Findings.—In seven cases all resected spinous processes from the dorso-lumbar region showed normal appearance; the other five showed mainly deposits of irregular bone on the tips. In one of the latter cases (pelvo-spondylitis of 5 years' duration), one spinous process also had small marginal osteolytic defects and ossification in the form of thin bone lamellae in an antero-posterior direction near the medial line, with a fissure 2 to 3 mm. wide in between, and a straight dorsal edge situated ventrally several millimetres below the tips themselves (Figs 1*a* and *b*, opposite).

Histological Findings.—The smaller arteries in the soft tissues adjacent to the bone showed more or less marked thickening of the walls with endarteritis obliterans. In eight of the twelve cases there were also clear signs in the soft tissues of an active inflammation, in the form of foci of round cells, frequently adjacent to small vessels, but sometimes diffusely distributed. These inflammatory cellular infiltrations were found not only in the connective tissue nearest the bony tissues—though they were most common there—but also sometimes in the surrounding fatty tissues and musculature. The inflammatory cellular infiltrations were in a few cases found to contain a number of leucocytes, in addition to round cells, but only an occasional eosinophilic leucocyte. The bony tissue adjoining the connective tissue showed, almost everywhere, signs of active processes of reconstruction. Thus, resorption had started in some areas, and in others new bone tissue was surrounded by osteoblastic layers (Fig. 2). These new bony structures were frequently found projecting from the normal border of the bone tissue into the surrounding connective tissue; we also observed, in the periphery of the bony structures, a tissue of osteoid type, fairly rich in cells and partially hyaline, and occasionally also areas of cartilage-like tissue. The fibrous connective tissue was in general very poor in cells.

In the case shown in Figs 1*a* and 1*b*, newly-formed bone tissue and osteoid tissue was observed in two islands, which were free from the spinous processes and connected with the interspinous ligament, lying not within it but on the boundary between the ligament and adjacent fatty tissues and musculature (Fig. 1*c*).

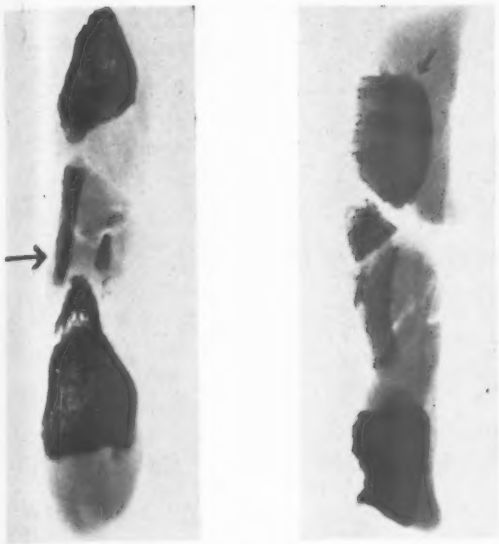

Fig. 1.—(*a*) Axial view and (*b*) lateral view of operation specimen composed of parts of spinous processes D12 and L1 with interjacent tissue. Note the small bone deposits on the distal spinous process (*b*) and dorsally a small inflammatory lytic defect (arrow); also the two parasagittal bone lamellae in the interspinous space.

Fig. 2.—Detail of border of spinous process L1 from same case as that seen in Fig. 1, showing formation of new bone.

Fig. 1.—(*c*) Histological section at the level of the arrow in (*a*) showing new bone islands on each side of the interspinous ligament.

C. Biopsies from Joints

(*i*) A 38-year-old male with a 21-year history of pelvo-spondylitis had changes in the hip joint with flexion contracture and almost no mobility; radiologically there was no synosteosis but a narrow joint space and a deformed caput. He was operated on by Judet's method at the Orthopaedic Clinic in Stockholm.

(*ii*) A 39-year-old male had considerable clinical signs and symptoms from the acromio-clavicular joint, with pain and restricted mobility, of relatively short duration. *X*-ray examination showed widespread destruction in the upper part of the joint, and in the periphery of this area new bone formation on the clavicular side (Figs 3*a* and *b*). The results of resection of the whole joint were excellent, and movement was completely painless.

Histological Findings.—Both joints showed active, chronic inflammation. In the acromio-clavicular joint (Figs 3*c* and *d*), the articular cartilage showed destruction and regressive changes in the upper part, the surface of the remaining cartilage being frayed and necrobiotic. In the lower part of the joint there was cartilage of normal height showing some superficial fraying, with patches of irregular stainability suggesting moderate, regressive changes. The bone at the level of the marked cartilage changes showed areas of destruction alternating with new bone formation. The lytic defects observed on the radiograph on the lower part of the clavicular side, in the immediate neighbourhood of the joint (Fig. 3*b*), was represented histologically by bone destruction with oedema and fairly plentiful round-cell infiltration in surrounding tissue (Fig. 3*d*). The

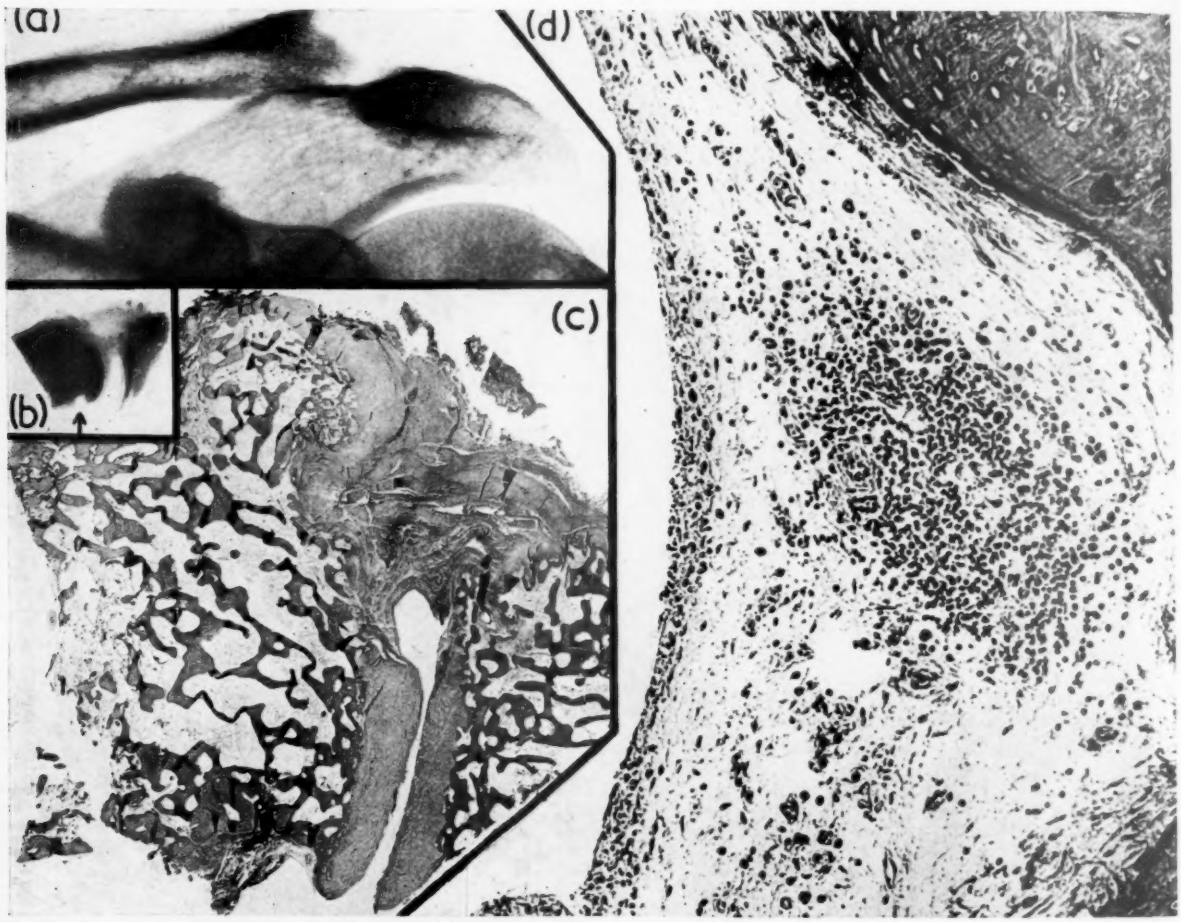

Fig. 3.—(*a*) Antero-posterior view of left acromio-clavicular joint in a case of pelvo-spondylitis ossificans of 12 years' duration, showing destructive lesion in upper part of joint and irregular bone formation on clavicle and acromion.
(*b*) Same joint after resection.
(*c*) Histological section from operation specimen showing localized destruction of articular cartilage and bone in upper part of joint; articular cartilage has retained its normal height and reveals only slight regressive changes in lower part.
(*d*) Detail from same section showing oedematous synovialis with marked round cell infiltration. This area corresponds to lytic defect in lower part of clavicular end (arrow, *b*).

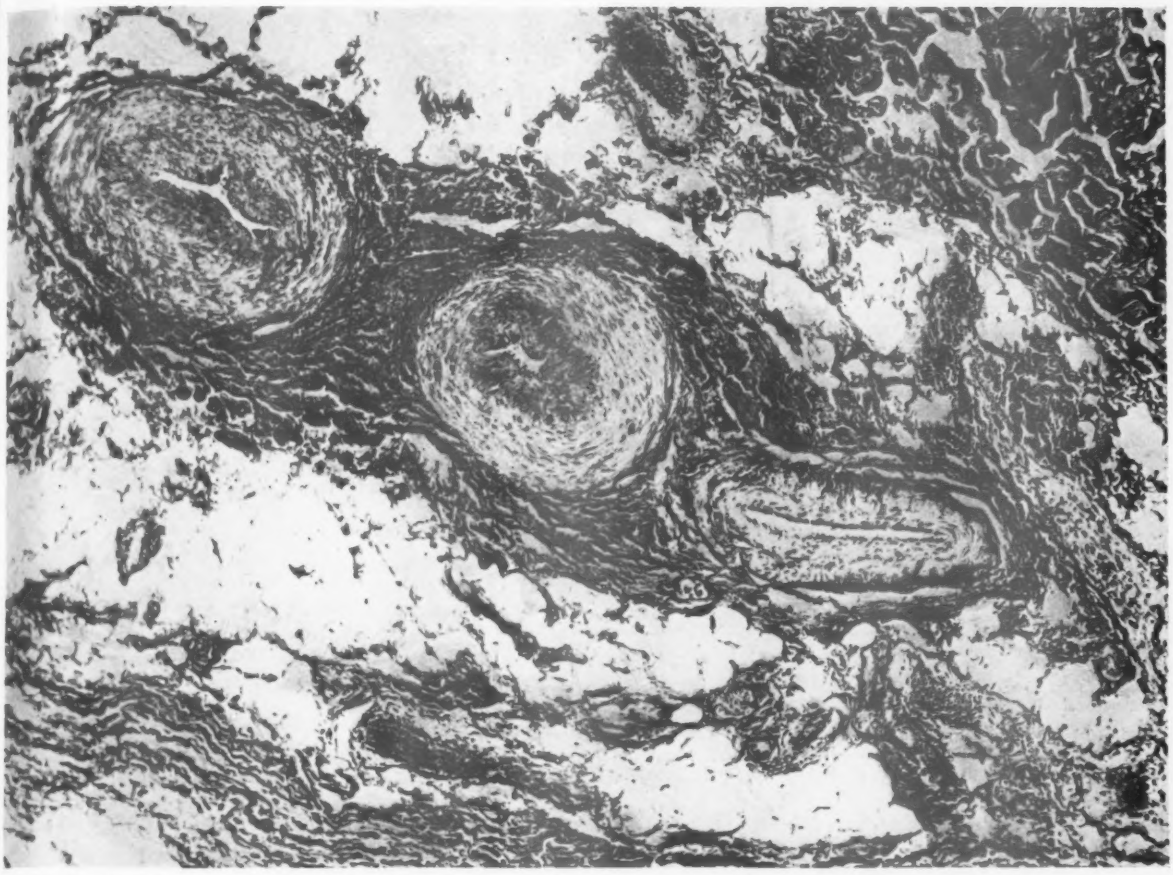

Fig. 4.—Section from biopsy specimen of periarticular tissue of hip joint in a case of pelvo-spondylitis ossificans. Note pronounced endarterial changes and small areas of round cell infiltration.

synovial layer was markedly changed, with patchy oedema and sclerosis, and highly vascular, with copious lympho-plasmo-leucocytic infiltrates. No eosinophilic leucocytes were found, and no fibrinoid necrosis. The small arteries had appreciably thickened walls. In the fatty and connective tissues round both joints there were foci of round-cell infiltration and endarteritic vascular change (Fig. 4).

D. Biopsies from Sternal Synchondrosis

In one case the subjective symptoms from the sternal synchondrosis were moderate; *x*-ray examition showed typical changes with irregular and blurred bone contours in the synchondrosis, and moderate sclerosis in the surrounding area. Histological examination showed inflammatory changes in the surrounding connective tissue; there were no inflammatory changes in the synchondrosis itself, but the bone-cartilage boundary was irregular with formation of new bone.

The second case, on the other hand, had both subjective symptoms and clinical signs, with tender swelling of the soft tissues. The *x*-ray changes were similar, but more marked, with central destruction the size of a hazel-nut, and concomitant signs of reparative, new bone formation dorsally (Fig. 5*a*). Histological examination showed marked inflammation both in the connective tissue and in the synchondrosis itself, with marked oedema and plentiful round-cell infiltration, as well as pronounced endarteritic change and destruction of cartilage and bone with patches of new bone formation (Figs 5*b* and *c*, overleaf).

Fig. 5.—(*a*) Lateral view of manubrio-sternal synchondrosis from a case of pelvo-spondylitis ossificans of 10 years' duration. Pronounced ventral and central bone destruction. New bone formation starting dorsally.

Fig. 5.—(*b*) Sagittal section from biopsy specimen of same manubrio-sternal synchondrosis showing cartilage with regressive changes and bone tissue with irregular border, with both bone destruction and new bone formation.

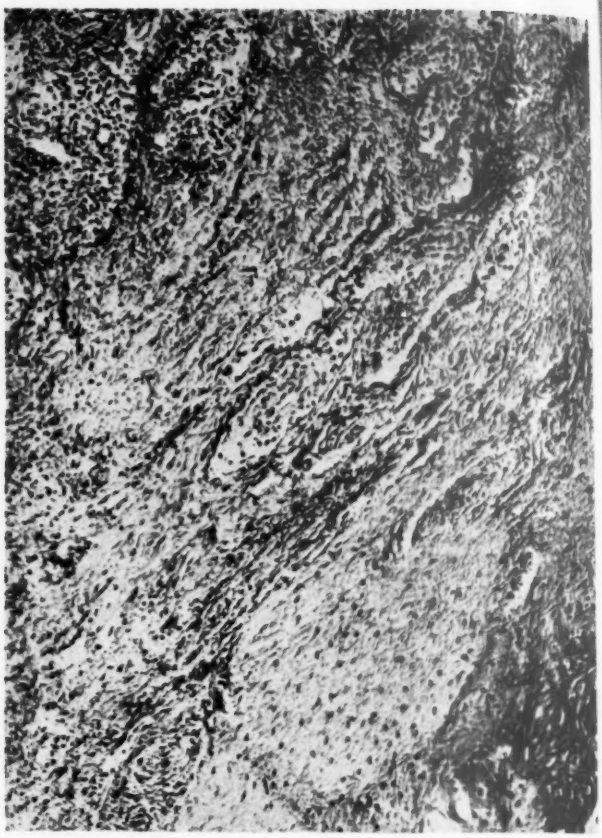

Fig. 5.—(*c*) Detail from same biopsy specimen, showing soft tissue with pronounced round cell infiltration adjacent to synchondrosis.

E. Biopsy from Intervertebral Disk

A 35-year-old male had synosteotic sacro-iliac joints and typical, partly-bridging syndesmophytes and anterior spondylitis in the dorsal spine, when signs of progressive "usual" disk degeneration developed (L5/S1), with radiating radicular pain. *X*-ray examination showed a narrowing of this disk space but no reactive spondylosis deformans on adjacent vertebral body margins or changes suggestive of pelvo-spondylitis. A transperitoneal operation was performed for this disk degeneration, with anterior fusion of L5/S1 and transplantation of blocks from the iliac crest. In the operation the anterior part of the disk L5/S1 was removed, together with anterior soft tissues, and adjacent parts of the vertebral bodies. Histological examination showed inflammatory changes with oedema, infiltration of inflammatory cells, and endarteritis, mainly in the areolar tissue on the ventral side of the disk (Fig. 6, opposite).

F. Spinal Autopsy

A 52-year-old male with advanced pelvo-spondylitis ossificans died after an operation for duodenal ulcer. The pelvo-spondylitic process had started more than 30 years earlier and was not in an active stage. In the pelvis there was osseous synosteosis with reconstruction of the sacro-iliac joints, remnants of the joint borders being still visible. There was typical, new bone formations bilaterally on the ischial tuberosities. *X*-ray examination of spinal specimens showed total paravertebral ossification round the whole periphery of the vertebral bodies in the dorsal and lumbar spine. The disks in the lower lumbar spine had decreased in height, and in the dorso-lumbar spine many disks were ossified. There was osseous synosteosis in all the apophyseal joints, but in some places in the lower dorsal spine traces of the joint borders could be seen. The costo-vertebral joints were also synosteotic. Apparently completely bridging bony structures were present between all the arches and the spinous processes. The very marked "band of sclerosis" seen in the frontal view of the lumbar spine in the median line was shown to be caused by highly eburneous, new-formed bone between the ventral halves of the spinous processes, not reaching dorsally to their tips, and thus not corresponding with the distribution of the interspinous ligament.

Histological Findings.—Osseous synosteosis was seen to be present in the majority of apophyseal joints, but in some places there were small islands of articular cartilage. The ligamentum flavum was bounded by small bony lamellae along its whole dorsal periphery, which is contrary to the normal finding. Occasional, small bone lamellae were seen towards the spinal canal, but the ligament itself appeared to be intact. No signs of inflammation were present. Even the anterior longitudinal ligament, apparently of normal thickness, could be seen on the ventral side of the bone bridges in the periphery of the discs.

G. Control Series for Comparison with Section A

Radiological Findings.—The spinous processes in the control series showed osteophytic deposits on the tips of most of the processes, of common "spondylosis" appearance. In no case was there ossification on the ventral side, either on the spinous processes or in the soft tissue between them, nor any osteolytic process. The average age in the control series was roughly 60, whereas that of the pelvo-spondylitis cases in Group A was 36 years.

Histological Findings.—There was no inflammatory cell infiltration. In some cases vascular changes of arteriosclerotic type were noted, but no endarteritis obliterans of the type invariably found in the pelvo-spondylitis series. Bony deposits were seen on the tips of the spinous processes in some cases, but no signs of marked bone reconstruction were found in these areas. These spurs were fairly sharply delimited from adjacent connective tissue, and no osteoid tissue was found.

Discussion

Histological examination of spinous processes and the iliac crest from pelvo-spondylitis cases of greatly varying duration showed changes which, on the whole, corresponded with the clinical and radiological phase of evolution. There was generally fibrous, more or less hyalinized tissue of connective type with transformation to cartilage and bone. The specimens from the younger patients also showed

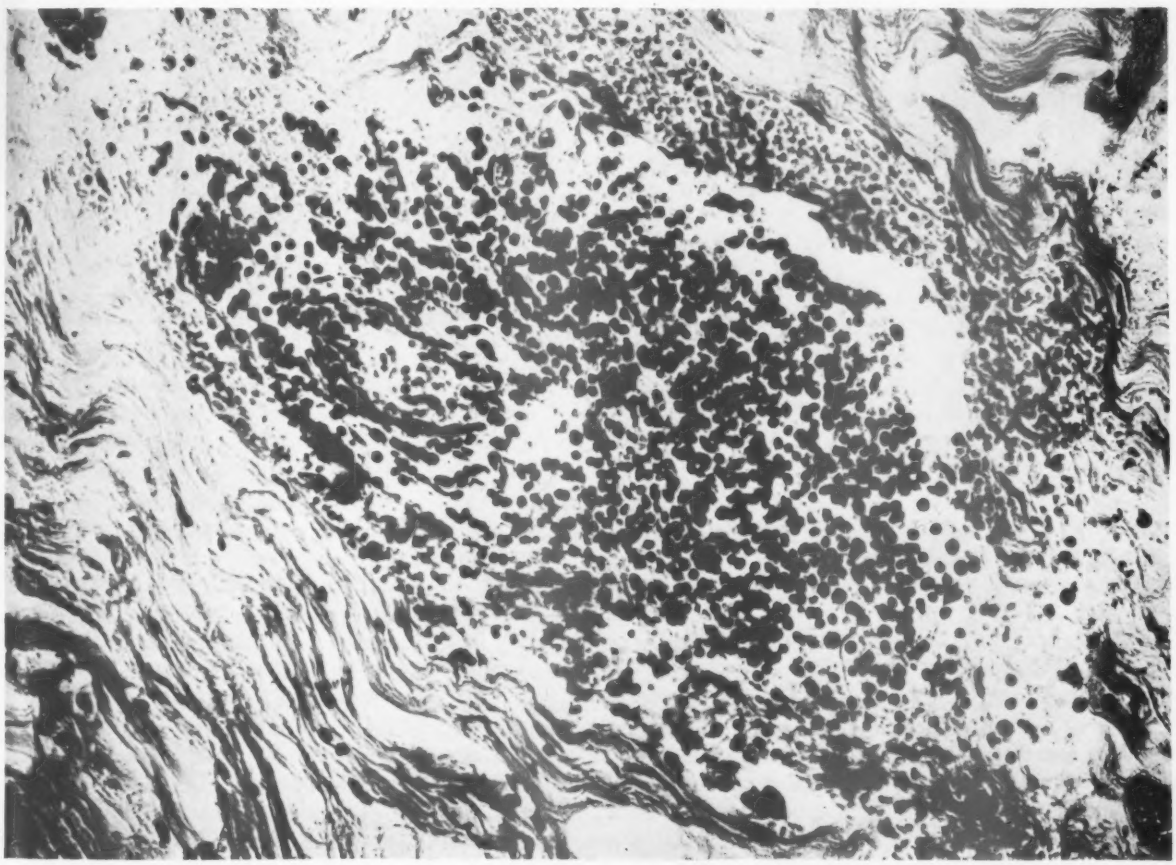

Fig. 6.—Round cell infiltration in connective tissue adjacent to intervertebral disk in a case of pelvo-spondylitis ossificans. Specimen obtained at a disk operation.

inflammatory cell infiltration near the bone and in the adjacent soft tissues, as well as signs of both superficial bone destruction and new formation of bone. The inflammatory changes were most pronounced in specimens from the newest—youngest—cases, less marked in those from older cases, and wholly absent in the oldest. Concurrently with the decrease in inflammatory changes there was a decrease in vascularity, increased hyalinization of the connective tissues, and more newly-formed bone. The case illustrated in Fig. 1 is of especial interest; here we see that new bone is formed not only on the surfaces of the spinous process but also as lamellae near the interspinous ligament, not within it but on the boundary between the ligament and adjacent muscular and fatty tissues. On the other hand, there were no signs of inflammation in the histological sections from spinous processes in the control group. The bony deposits on their tips were fairly clearly delimited from the adjacent soft tissues, and no marked signs of bone reconstruction or osteoid tissue were found.

Two joints, one of the manubrio-sternal synchondroses, and the specimen from a lumbar disk showed the same type of change, marked chronic inflammation with cartilage and bone destruction, but also new formation of bone. In the second manubriosternal synchondrosis, which came from a patient with only moderate, current clinical signs of inflammation, there was only a focal infiltration of lymphocytes in the neighbouring connective tissue and some oedema in the periosteum; there were no inflammatory changes in the synchondrosis itself, in which the bone-cartilage boundary was irregular. The cartilage was in patches regressively changed and there was formation of new bone.

The longstanding case which came to autopsy showed no signs of inflammation. Most of the apophyseal joints were synosteotic, though slight traces of the articular cartilage remained in places. The completely bridging bone between the arches, seen in the radiograph, was found to be due to ossification only in the periphery of ligamentum flavum, chiefly on the dorsal side, while the ligament itself was mainly normal (Fig. 7). The anterior longitudinal ligament was also in the main unchanged, and the bridging ossification was situated on its dorsal side (in the periphery of the disks).

More or less pronounced endarteritis was found in all the specimens from the pelvo-spondylitis cases, whether the patients had been given radiotherapy in this region or not. The significance of endarteritis obliterans, demonstrated earlier by Cruickshank (1951) in diarthrodial joints, is still open to discussion as regards pelvo-spondylitis.

Fig. 7.—Longitudinal section of ligamentum flavum from autopsy of advanced stationary pelvo-spondylitis ossificans. Note bone formed at outer periphery of ligament.

No eosinophilia, fibrinoid necrosis, or changes which may be signs of rheumatic or allergic reaction were found in the specimens examined, nor any signs of any other specific processes.

The non-specific chronic inflammation in the paravertebral connective tissue, disk, and sternal synchondrosis corresponds to the changes demonstrated by Cruickshank in diarthrodial joints. As our biopsy specimens were taken from patients in whom the duration of the disease varied greatly, certain conclusions may be drawn as to the evolution of this inflammatory process and its connection with later ossification. Primarily, there is an inflammatory phase with bone destruction. These changes represent an earlier phase in evolution than that seen in the cases already described in the literature. They later regress while the connective tissue shows

hyalinization and bone formation occurs. Earlier investigations of intervertebral disks and of the manubrio-sternal synchondrosis (Savill, 1951; Hart and others, 1949) represent this later phase of ossification after the inflammation has disappeared.

Many authors have shown that the anterior ossification between the vertebral bodies is situated not in the anterior longitudinal ligament, but in the periphery of the disks. We have found that other so-called "ligamentous" ossification is not localized primarily in the ligaments. As in other types of ossification in pelvo-spondylitis, these are preceded by an inflammatory phase localized not in the fibrous, poorly vascularized ligament and disk tissues, but in the neighbouring areolar tissue—between the interspinous ligament and the deep muscles of the back, or between the anterior longitudinal ligament and the disk with adjacent vertebral body margins. In these areas ossification appears later, and this involves the ligament itself only in very advanced cases.

The morphological changes clearly corresponded with the clinical and radiological findings. Clinical signs of an active process, in the form of swelling in the soft tissues and tenderness over the skeletal parts, were represented radiologically by a more or less marked blurring of the bone contours and the presence of lytic defects which, histological examination showed to have been caused by inflammatory bone destruction. Bone-forming processes have been demonstrated both radiologically and histologically at a remarkably early stage at the same time as the inflammatory changes. In later phases, clinical symptoms, such as rigidity without local irritation, have been represented by ossification with even bone contours and altered structure both radiologically and histologically.

As mentioned earlier, the radiologically demonstrable evolution was similar in the various skeletal localizations in pelvo-spondylitis. It would, then, appear likely that the morphological basis is the same in sites less accessible for biopsy, such as the vertebral bodies.

The correspondence demonstrated between clinical, radiological, and histological changes widens our understanding of the nature of the disease and gives us an explanation of its usual course. It is chronic but intermittent, with, at first, intervals between exacerbations wholly, or almost wholly, free of symptoms. The specimen from the acromio-clavicular joint, which was taken during an unusually severe exacerbation, illustrates this characteristic mixture within the same joint of a high degree of inflammatory destruction of bone and cartilage together with new bone formation, other parts of the joint being practically unaffected and the cartilage thickness unchanged.

This normal thickness in the articular cartilage, seen in *x*-ray pictures, or perhaps more correctly the relatively unchanged distance between the bone borders in a joint (or synchondrosis as in the sternum or between the vertebral bodies), has been described as typical of pelvo-spondylitic involvement of the hip joint (Jacqueline, 1952), even if it progresses to such a degree as to lead to osseous ankylosis. In synosteotic joints this corresponds to the radiological and histological findings of scattered islands of cartilage of considerable thickness, as in the sacro-iliac joints, the apophyseal joints, and even the hip joints.

This evolution and its end result differentiates arthritic joints in pelvo-spondylitis from the rapid, total cartilage destruction in joints affected with acute septic infection, from the diffuse destruction of peripheral rheumatoid arthritis, and from the more gradual destruction of tuberculosis.

The histological changes allow a better understanding of the clinical and radiological evolution described above. The inflammatory process is local and leads to more or less complete destruction, but soon the inflammatory character is replaced by local healing and new bone formation. This occurs in certain restricted areas in the sacro-iliac joints, in synchondroses, and in the areolar paravertebral connective tissue. It would appear, then, that the inflammatory process, as also the subjective symptoms and the radiological changes, occurs in acute exacerbations of a chronic disease whose course, however, is intermittent, with intervals wholly free of symptoms at first.

What, then, is the cause of this intermittent inflammation, and why does it occur in the sacro-iliac joints and later in the paravertebral connective tissue and the pelvis, attacking bone, joints, and synchondroses mostly from the surface and with a mainly ascending tendency in the spine? Clinical studies (Romanus, 1953) suggest that the cause of pelvo-spondylitis is usually a chronic, non-specific infection in the prostate, and particularly in the seminal vesicles. Prostato-vesiculitis was present in practically every case in the series of 117 men examined urologically. The manifestation and evolution of the urogenital infection and the pelvo-spondylitis showed striking correspondence in many cases. The spread of infectious-toxic products of chronic prostato-vesiculitis and the routes they follow, particularly the so-called vertebral venous system (Batson, 1940, 1942a, b), gives us a clear anatomical basis to explain the distribution of the pathological changes described above. Dissemina-

tion from these glands *via* the general circulation accounts for the common occurrence of general attacks with iritis and other eye symptoms and involvement of peripheral joints, as in the complete so-called Reiter's syndrome. This aetiological and pathogenetic conception clarifies a number of features in pelvo-spondylitis, its predominance of men, its onset at the age of about 20, and the presence of colon-rectum diseases (*e.g.* dysentery), and the appearance of similar skeletal changes in cases of Brucellosis and in patients with paraplegia.

Summary

The results of histological examination of nineteen biopsy specimens and one autopsy case of pelvo-spondylitis ossificans (ankylosing spondylitis) are reported in detail. The clear correspondence between the histological, radiological, and clinical findings is pointed out. A brief description is given of the radiological evolution of the disease, and its nature, pathogenesis, and aetiology are discussed.

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Etude histologique en corrélation avec l'aspect clinique et radiologique de la *pelvo-spondylitis ossificans*

Résumé

On rapporte en détail les résultats de l'examen histologique des prélèvements dans un cas d'autopsie et chez dix-neuf malades atteints de *pelvo-spondylitis ossificans*. On montre le rapport étroit entre les résultats histologiques, radiologiques, et cliniques. On décrit brèvement l'évolution radiologique de la maladie et on en discute la nature, la pathogénie, et l'étiologie.

Estudio histológico de la *pelvo-spondylitis ossificans* en correlación con los hallazgos clínicos y radiológicos

Sumario

Se relatan detalladamente los resultados de estudio histológico en diecinueve casos de biopsia y en un caso de autopsia de enfermos con *pelvo-spondylitis ossificans*. Se demuestra la relación estrecha entre los resultados histológicos, radiológicos, y clínicos. Se describe brevemente la evolución radiológica de la enfermedad y se discute su naturaleza, patogenesis, y etiología.

RARE FEATURES IN A CASE OF GAUCHER'S DISEASE

BY

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Descriptions of the osseous lesions in Gaucher's disease have been published from the clinical, radiological, and pathological point of view. The most common sites of these lesions are the hip-joint (*e.g.*, Brill and others, 1905; Todd and Keidan, 1952; Vaughan-Jackson, 1952; Wood, 1952), the mandibular joint (Cecil, 1948; Snapper, 1943), and the knees (Draznin and Singer, 1948; James, 1952; Kroboth and Johnson, 1952; Markovits, 1949; Pick, 1927), including the lower part of the shaft of the femur with its typical flask-like deformity (Davies, 1952; Windholz and Foster, 1948). Affections of the shoulder bones seem to be less frequent; Pick (1927), reviewing the literature as a pathologist and adding four cases of his own, does not mention involvement of the upper extremity except in the case described by Brill and others (1905). Apart from these, we have found only four cases with lesions at this site in the literature available to us (James, 1952; Kroboth and Johnson, 1952; Morgans, 1947; Snapper, 1943). Pre-existing osseous affections are prone to deterioration after splenectomy according to Snapper (1943), but the development of new osseous lesions after this operation has been described only rarely (Meakins, 1950; Todd and Keidan, 1952; Vaughan-Jackson, 1952), and then usually a few months to 2 years after removal of the spleen (Windholz and Foster, 1948; Wood, 1952).

Finally, to the best of our knowledge, the almost simultaneous appearance of clinical manifestations of rheumatic fever and bone lesions due to Gaucher's disease have not been recorded.

Our case showed, in addition to the rare features indicated above, a relatively good response to simple physical treatment, and it was therefore thought worth while to report it.

Case Report

A **31-year-old baker,** of German-Jewish origin (No. 144608/1953), married and with two healthy children, migrated to Palestine in 1933 at the age of 21. His family history was irrelevant.

Previous Medical History.—At the age of 3 years an enlarged spleen was found and the tentative diagnosis of Gaucher's disease was made.

In December, 1937, when he was 25 years old, a splenectomy had been performed in another hospital in Palestine; the pathological report described a very large spleen and the clinical diagnosis was confirmed by histological examination. Before operation the number of thrombocytes was 40,000 per c.mm.; after the operation this increased to 1,170,000, and normal levels returned within a few weeks. The post-operative course was uneventful and the patient felt well for the next 10 years.

In 1947 he contracted infective hepatitis, was hospitalized, and returned to work after 6 weeks.

In August, 1951, he fell ill with a typical rheumatic fever and was treated in the Haifa Government Hospital; slight cardiac involvement developed at this time, but he reacted well to salicylate treatment, and when discharged on October 3, 1951, was in good general condition, but still showing a rather high blood sedimentation rate (60 mm./hr (Westergren)). At this time *x*-ray examination of the bones (including the humerus), showed no abnormalities, but a bone-marrow puncture revealed many typical Gaucher cells.

Six months later, the patient developed a swollen right ankle after having slipped in the street, and shortly afterwards a slight swelling of the left ankle interfering with locomotion. In addition, severe pain was felt in both knees, accompanied by restriction of movement. Several orthopaedic surgeons advised him to have the menisci removed, but the patient refused surgery. He was given short-wave diathermy and ultrasonic therapy with only doubtful improvement. During the course of this treatment, in July, 1952, severe pain was felt in the right shoulder, and an *x* ray revealed destructive changes in the head of the right humerus. He received treatment with ACTH and cortisone, which afforded only slight relief for a very short period.

In May, 1953, his tonsils were removed, and treatment with autovaccine was given, without satisfactory results.

In August, 1953, the patient was seen in our Out-

Fig. 1.—Radiograph of shoulder, showing partial destruction of proximal end of humeral head.

Fig. 2.—Radiograph of elbow, lateral view.

Fig. 3.—Radiographs of knees, antero-posterior view.

Patient Department, having been unable to work for the last 4 months.

General Examination.—He appeared ill-nourished; his face was greyish-yellow and spotted with brown pigment which was also present on the arms and legs; there were pingueculae of both sclerae, marked hypometropia, and bilateral exophthalmos; a movable firm gland of cherry size was palpated in the right axilla; the thyroid was not enlarged. In the heart the first sound at the apex was prolonged and muffled, P_2 accentuated, blood pressure 120/80 mm. Hg. The liver was smooth and palpable 4 cm. below the costal arch. There were no other internal or neurological abnormalities.

Joints.—The right shoulder had almost no movement and severe atrophy of all shoulder muscles was found.

The left elbow had extension of 160° only, very slightly restricted flexion, painful on movement.

The left knee was some degrees short of full extension, and slightly tender on movement.

The other joints (including the hips and mandibular joints) showed no abnormality.

Laboratory Findings:
Albumin: traces.
Blood sedimentation rate: 8 mm./hr (Westergren).
Blood count: erythrocytes 3,700,000; haemoglobin 12 g. per cent.; leucocytes 14,000/c.mm.; thrombocytes 122,000; coagulation time 3 min.; bleeding time 1 min.; neutrophils 48 per cent., lymphocytes 42 per cent., eosinophils 6 per cent., monocytes 4 per cent. (target cells?).
Blood chemistry: cholesterol 250 mg. per cent., prothrombin time 61 per cent., phosphor 3·3 mg. per cent., thymol turbidity test 2-3, cephaline 0, Takata Ara 0.

X-ray Findings:
Heart: Slight dilatation of left ventricle; questionable configuration of mitral heart.
Lung fields: Not abnormal.
Joints: Right shoulder: condensed areas with partial destruction of proximal end of humeral head, articular surface being hazy. No change in glenoid fossa (Fig. 1).
Left elbow: head of radius dislocated in frontal direction at epiphyseal line; anterior articular space narrowed (Fig. 2).
Lumbar spine: spotty condensation of L4, its upper border not sharply defined; L3 intervertebral space narrowed (anterior-posterior and lateral view).
Sacro-iliac joints: border of left joint not sharp, showing small cystic defects, particularly in lower parts.
Femora: no dilatation of distal shaft visible on either side.
Knee joints: sharpening and prominence of eminentia intercondyloidea in both knees, some unevenness of articular surface of both tibiae, particularly medially and anteriorly (Fig. 3).
No other joints showed abnormalities.

Treatment was undertaken cautiously. Peri-articular novocaine infiltration was given to the shoulders and knees, and heat application and progressive remedial exercises were begun. To our surprise, 3 weeks after having started therapy, the patient was able to raise his right arm to 90° in forward flexion, and to 45° in abduction. Even rotation was possible to more than 20″. The right knee could be almost fully extended. His pains disappeared almost entirely; he walked freely for more than half an hour at a stretch, and he was able to use his right arm to a considerable extent. He was advised to return to work and to continue the exercises at home, and 4 months after discharge his movements showed no deterioration. He has resumed work in his profession at full capacity.

Discussion

This case showed some unusual features:

(*a*) The disease affected the humeral-acromial joint and caused complete incapacity.

(*b*) The involvement of the bones occurred 17 years after splenectomy, a sequel which has not been reported until now.

(*c*) Rheumatic fever occurred almost simultaneously with the appearance of symptoms in the shoulder which were due to Gaucher's disease. It could not be determined whether the rheumatic fever predisposed to the development of bony Gaucher's disease, promoting it as a kind of trigger mechanism, or whether it was a coincidental event.

(*d*) Degenerative osteo-arthritic changes were also encountered in some joints at the same time.

The patient was treated in the same way as any other "frozen shoulder" in our department by heat, novocain infiltration, and simple exercises, and he was able to return to work after a short course of this therapy (Adler, 1948; Adler and Grossmann, 1946).

Summary

(1) The literature on Gaucher's disease affecting the osseous system is surveyed briefly.

(2) A case is presented in which clinical bone manifestations and degenerative osteo-arthritis began after a bout of rheumatic fever which occurred 17 years after splenectomy.

(3) Several unusual aspects of this case are stressed: the rare involvement of the shoulder joint; the development of osseous lesions many years after splenectomy; the simultaneous appearance of rheumatic fever and bony manifestations of Gaucher's disease.

(4) The response to physical treatment and the possibility of rehabilitation are emphasized.

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Rares traits d'un cas de maladie de Gaucher

RÉSUMÉ

(1) On passe brèvement en revue la littérature sur la maladie de Gaucher affectant le système osseux.

(2) On présente l'observation d'un cas où les manifestations osseuses et de dégénérescence ostéo-arthritique avaient débuté après une attaque de rhumatisme articulaire aigu, celui-ci survenant 17 ans après la splenectomie.

(3) On souligne plusieurs aspects rares de ce cas: implication rare de l'articulation de l'épaule; apparence des lésions osseuses bien des années après la splenectomie; apparence simultanée du rhumatisme articulaire aigu et des manifestations osseuses de la maladie de Gaucher.

(4) On met en relief la reponse à la physiothérapie et la possibilité de rehabilitation.

Raros rasgos de un caso de enfermedad de Gaucher

SUMARIO

(1) Se pasa en revista la literatura sobre la enfermedad de Gaucher afectando el sistema óseo.

(2) Se presenta un caso en que las manifestaciones óseas y osteoartríticas degenerativas empezaron después de un ataque de reumatismo poliarticular agudo el cual ocurrió 17 años después de la esplenectomía.

(3) Se subraya varios aspectos raros de este caso: implicación poco común de la articulación del hombro; desarrollo de las lesiones óseas muchos años después de la esplenectomía; aparición simultánea del reumatismo poliarticular agudo y de las manifestaciones óseas de la enfermedad de Gaucher.

(4) Se acentua la respuesta a la fisioterapia y la posibilidad de rehabilitación.

SODIUM SALICYLATE AND PROBENECID IN THE TREATMENT OF CHRONIC GOUT*

ASSESSMENT OF THEIR RELATIVE EFFECTS IN LOWERING SERUM URIC ACID LEVELS

BY

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Very little is known about the aetiology of acute attacks of gout or the mode of action of colchicine in relieving them. Their relationship to high serum uric acid levels and urate deposition is obscure, for maintaining serum levels at normal together with a negative urate balance does not prevent their occurrence. Fortunately the vast majority of acute attacks readily respond to colchicine in proper dosage, and the few exceptions may be treated with phenylbutazone ("Butazolidin").

Unlike the acute variety, chronic gout appears to be closely related to high serum and tissue fluid uric acid levels with supersaturation and deposition of urates in various tissues, especially joint structures and bursae. Uric acid deposition induces a chronic inflammatory reaction, and increasing size of the deposits leads to progressive and even total destruction of the affected joints. Urate deposition is often confirmed by the presence of tophi, but even in their absence it may be inferred by isotopic uric acid dilution studies. Such studies have shown that the miscible pool of uric acid in normal adults ranges from 731 to 1,341 mg. (Benedict, Forsham, and Stetten, 1949; Geren, Bendich, Bodansky, and Brown, 1950; Bishop, Garner, and Talbott, 1951). In gouty persons the miscible pool is greatly increased and may be as high as 30,000 mg. (Benedict and others, 1950). This enormous increase cannot be accounted for by uric acid in solution and must indicate the presence of solid phase urate which has taken part in dilution of the isotope.

The patient with chronic gout complains of increasing stiffness, pain, and deformity of one or more joints, symptoms which are unaffected by colchicine and which ultimately give rise to severe crippling and invalidism. Until 1950, it had not been found possible to maintain the serum uric acid at normal levels, and the progress of chronic gouty changes had never been arrested. Since 1950, however, the continuous administration of sodium salicylate or probenecid ("Benemid") has been shown to maintain a prolonged lowering in the serum uric acid levels, and this has proved of great value in the treatment of chronic gout.

The effect of sodium salicylate in increasing urinary uric acid excretion in gouty persons has been known since 1877, and its ability to reduce the serum uric acid since 1914. When given continually it is a most useful drug in maintaining the serum uric acid of chronic gouty persons at a normal or near normal level, an effect which persists for upwards of 3 years and is accompanied by complete or very marked improvement in the symptoms and signs of the disorder (Marson, 1952, 1953a). The lowering of serum uric acid levels is accompanied by mobilization of deposited urate, as shown by shrinkage or total disappearance of tophi, recalcification of areas of bone absorption, and a prolonged increase in the urinary uric acid levels (Marson, 1952, 1953a). Isotopic studies have shown a marked diminution in the metabolic pool of uric acid during salicylate therapy (Benedict and others, 1950). The delayed recognition of the beneficial effects of sodium salicylate may have been due to the following reasons:

(1) Gutman (1950) and Talbott (1953a) rejected continuous administration of salicylate because the early development of toxic symptoms prevents adequate dosage. It has been shown, however, that, although most patients suffer salicylism initially, a majority develop a tolerance within 1-6 weeks, and thereafter are able to take the required dosage with no more than occasional and minor symptoms (Marson, 1953a).

(2) Bauer and Klemperer (1944) reported that the effect of salicylate on depressing the serum uric acid is short-lived. This assertion has since been disproved and patients have maintained marked lowering of serum uric acid for periods of upwards of 3 years.

(3) Jennings (1937) reported that normal levels of blood uric acid could be maintained by administering sodium salicylate in a daily dosage of 80 gr. 3 or 4 days

* This paper is based on a communication to the Heberden Society on May 7, 1954.

a week. Bauer and Klemperer (1944) and Marson (1953a) were unable to confirm this finding. Such intermittent therapy has never been shown to arrest chronic gouty changes.

Wolfson and others (1948) reported that caronamide (4′-carboxyphenyl-methanesulphonanilide) increased uric acid excretion in normal subjects, and Gutman (1950) reported the use of this drug in thirteen gouty subjects. With a daily dosage of 12 to 13·5 g. a marked lowering in the serum uric acid levels resulted. However, the large number of tablets consumed daily was objectionable, and various toxic reactions occurred, including gastrointestinal symptoms, drug fever, and drug rash. This drug is no longer used.

A new benzoic acid derivative, probenecid ("Benemid": p-(di-n-propylsulfamyl)-benzoic acid), structurally related to caronamide, introduced into clinical medicine by Boger and others (1950), was found to have a marked effect on blocking the tubular secretion of penicillin, para-aminosalicylic acid, para-aminohippuric acid, and phenolsulphonphthalein. It was later shown to block tubular reabsorption of certain glomerular constituents (Schneider and Corcoran, 1950) including uric acid (Gutman, 1950). These effects were similar to those obtained with caronamide but could be obtained with a much smaller dosage, 2 g. probenecid being equivalent to 24 g. caronamide. Since that time various reports have been published on the value of probenecid in the treatment of chronic gout, and there can be no doubt that, in a daily dosage of 2 g., it causes a marked lowering in serum uric acid levels, a marked initial increase in urinary uric acid excretion, and great general improvement in chronic gouty patients. It also causes a shrinkage in the metabolic pool of uric acid (Bishop, Rand, and Talbott, 1951).

Gutman (1950, 1951a) reported a series of fourteen patients in whom probenecid in a daily dosage of 2 g. caused a mean increase in urinary uric acid excretion of 58·5 per cent., and a sustained fall in serum uric acid to approximately half the initial level. In a series of fifteen patients a dose of 1 g. daily produced a mean decrease of 24 per cent. in serum level (Gutman, 1951b). Pascale and others (1952) reported that in seventeen gouty subjects 2 g. probenecid daily induced a fall in the serum uric acid level at the end of 72 hrs to 42-70 per cent. of previous levels with an average fall to 55 per cent. Impaired renal function was demonstrated in three further subjects in whom probenecid failed to lower the serum uric acid. Two illustrations (Talbott, 1953b) demonstrate the effect of probenecid on serum uric acid levels in two of a large series of patients, but it is not stated whether these are representative of the whole series, nor is the dosage of probenecid recorded. The first case was treated for 26 months and the average serum levels were approximately 8·65 mg. during a control and 4·66 mg. during probenecid treatment (a fall to 54 per cent. of initial levels). Talbott stated that the lowest uric acid figure (3·0 mg.) was noted within the first month of treatment. The second patient received probenecid for 14 months, and the serum level fell from an initial average of 9·5 mg. to an average on probenecid of 6·5 mg. (a reduction to 68·4 per cent. of the control level).

It has been reported that when salicylates are given concomitantly with probenecid the uricosuric effect is nullified (Gutman and Yü, 1952). Pascale and others (1952) found that, whereas 2 g. probenecid daily effected a marked lowering in the serum uric acid level in gouty patients, the addition of 1·3 g. acetylsalicylic acid 6-hrly nullified this effect.

It would appear likely that the beneficial effects of both probenecid and salicylates are dependent upon the lowering of serum (and tissue fluid) uric acid levels, with arrest of further deposition of urate and partial reabsorption of deposits. If this hypothesis is correct it becomes important to assess the relative merits of salicylate and probenecid in lowering the serum uric acid level, and an attempt to do this is recorded below.

Patients Investigated and Methods

A series of 21 chronic gouty patients has been studied closely over the past 45 months, and an attempt has been made to maintain a continuous lowering in the serum uric acid levels with either salicylates or probenecid therapy.

The diagnosis of gout was based upon a history of attacks of acute arthritis, the witnessing of one or more such attacks together with response to colchicine therapy (0·5 mg. 2-hrly until pain disappears or diarrhoea occurs), and a raised serum uric acid level. Approximately half the patients had demonstrable tophi and a further half had a family history of gout. The patient was judged to be suffering from chronic gout if the joint pain had persisted for longer than 3 months and was unaffected by a course of colchicine therapy.

All patients had a minimum of three estimations of the uric acid before therapy and were advised to take a normal diet and an increased fluid intake. They were all supplied with crystalline colchicine tablets (0·5 mg.) with instructions to treat all acute episodes with one tablet 2-hrly until the pain has disappeared or diarrhoea occurred. They then commenced salicylate or probenecid therapy and were usually admitted to hospital for close study at this time. After discharge they attended a gout clinic at intervals of not longer than a month, and at each visit progress was recorded, uric acid estimated, and the appropriate therapy prescribed.

Some patients received salicylate continuously (Cases 1-17) and others probenecid (Cases 18-21). Four (Cases 8, 15, 19, 11) received both drugs at different times. Sodium salicylate was administered in a daily dosage of 60-120 gr. (usually 90 gr.), normally equally spaced in three doses. At first it was combined with an equal dose of sodium bicarbonate, but more recently it was usually dispensed alone as a fluid with a flavouring agent and sodium sulphite as a preservative. The patient received a freshly dispensed mixture at each visit and it was never administered for longer than one month. Probenecid was administered in a daily dosage of 2 g. equally spaced over four doses.

Uric acid determinations were performed by the colorimetric method of Brown (1945). Estimations in one hundred non-gouty persons (Marson, 1953a) had shown a mean serum uric acid of $4{\cdot}54 \pm 0{\cdot}15$ mg. per 100 ml. in males, and $3{\cdot}82 \pm 0{\cdot}14$ mg. per 100 ml. in females.

In addition to the long-term investigations, it was felt advisable to assess results after single doses of sodium salicylate and probenecid. The patients selected for this trial were a female aged 60 yrs, suffering from rheumatoid arthritis, and three males, aged 59, 47, and 42 yrs, two with gout and one with rheumatoid arthritis (Cases I-IV).

All these subjects were in hospital receiving normal mixed diets with the exclusion of any high purine foods. No drugs were administered except on the test days; on these days the subjects remained in bed, and their diet and fluid intake was limited to 10 oz. milk at 7 a.m., 11 a.m., 1 p.m., and 3 p.m. The bladder was emptied at 7 a.m. and thereafter 2-hrly until 3 p.m. The test days were as follows:

(*a*) *Control.*—10 oz. water at 9 a.m.
(*b*) *Sodium Salicylate.*—100 gr. freshly prepared, administered orally in 10 oz. water at 9 a.m.
(*c*) *Probenecid.*—2 g. with 10 oz. water at 9 a.m.
(*d*) *Sodium Salicylate.*—100 gr. with 2 g. probenecid and 10 oz. water at 9 a.m.
(*e*) *Probenecid.*—4 g. with 10 oz. water at 9 a.m. (two subjects only).

All test days were separated by at least 3 clear days. The 2-hr urine samples were tested for uric acid (Bidmead, 1951), and creatinine (Folin, 1914); Fig. 7 shows mean results expressed as uric acid : creatinine ratios. It was assumed that neither drug has any significant effect upon creatinine excretion. A similar technique has been used in assessing the relative uricosuric effects of ACTH and sodium salicylate (Marson, 1953b).

Estimations of serum salicylate were done in six subjects (Cases A-F) in similar circumstances to the patients on test day (*b*). The serum salicylate was estimated by the method of Smith and Talbott (1950).

In another individual (Case X), not one of the series of 21, a further investigation was carried out to assess the results of combining probenecid administration with salicylate. The subject was male, aged 42 years, and suffered from chronic gout. He was in hospital and received a normal mixed diet with the exclusion of high purine foods. The serum and total urinary uric acid were estimated daily and, after an initial control period, sodium salicylate was administered in a dosage of 30 gr. 8-hrly. This was continued, and after 8 days, probenecid was also administered in a dosage of 0·5 g. 6-hrly and the tests continued for a further 8 days (Fig. 8).

Results

Seventeen chronic gouty patients received continuous salicylate therapy for periods of 9-45 months. During this time the serum uric acid was estimated at least once every 4 weeks. Table I shows the

TABLE I

SERUM URIC ACID LEVELS IN SEVENTEEN PATIENTS WITH CHRONIC GOUT BEFORE AND DURING SODIUM SALICYLATE THERAPY

Case No.	Duration of Therapy (months)	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)
		Initial			During Therapy			
		Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations	
1	45	7·8	5	2·43	4·1	46	1·63	52·6
(Fig. 3) *2	42	7·5	8	3·85	2·6	64	0·59	34·7
3	41	5·0	22	0·33	3·4	78	1·29	68·0
(Fig. 2) 4	41	4·8	17	0·67	2·2	47	0·74	46·2
5	34	8·5	3	0·51	4·2	47	1·68	49·4
6	32	8·2	17	0·73	3·4	27	1·09	41·5
7	30	6·8	7	0·62	5·3	72	1·53	77·9
(Fig. 6) 8	27	8·6	14	1·41	3·3	34	0·81	38·4
9	24	9·1	3	2·72	3·6	35	1·09	39·6
10	19	7·5	3	0·53	5·1	31	1·10	68·0
11	18	10·6	35	2·12	6·1	77	1·72	57·5
12	15	9·3	4	1·43	2·9	14	0·79	31·2
13	14	7·4	11	1·50	5·0	40	1·29	67·6
14	13	6·8	10	0·34	4·2	11	1·02	61·8
(Fig. 5) 15	12	5·0	9	0·50	1·8	15	0·31	36·1
16	11	9·0	13	1·02	4·1	11	0·19	45·6
17	9	6·3	6	0·91	2·3	12	0·86	36·7
Average	25							50·2

* In Case 2, sodium salicylate was replaced by aspirin during 27 months.

mean uric acid levels before and during therapy; the figures in the last column indicate the extent of therapeutic lowering of the uric acid concentration. Uric acid estimations during the first 3 weeks of therapy have not been included. The Table includes all patients treated at the clinic with continuous salicylate administration for a minimum period of 9 months, with the exception of two in whom a raised blood urea was present and therapeutic depression of serum uric acid levels was found impossible, and a further two whose co-operation was insufficient to justify inclusion in this study. It is seen that in six of the seventeen patients the uric acid was maintained at an average of less than 40 per cent. of the pre-treatment figures, and in a further four patients at a level below 50 per cent. of the initial level. The percentage fall with salicylate bears no relationship to the initial level (Fig. 1). In only four of the seventeen patients was it found impossible to maintain the level below the mean for normal persons. The four exceptions comprised the three patients in whom salicylism was troublesome and the fourth patient was the most jovial but probably least reliable of the series.

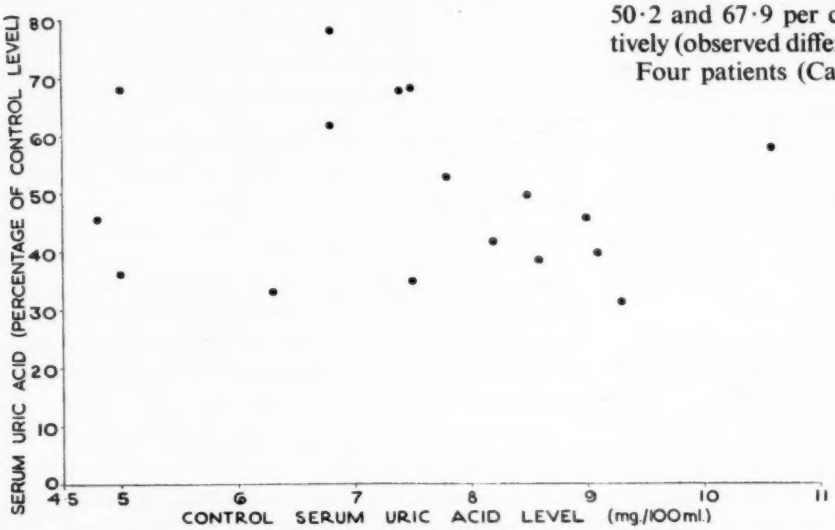

Fig. 1.—Serum uric acid levels in seventeen patients during prolonged salicylate therapy (percentage of control levels).

Table II illustrates similar figures for six chronic gouty patients (Cases 11, 15, 18-21) to whom probenecid was administered continuously for periods of 12-19 months. In no patient was it found possible to maintain the serum uric acid at a mean level below 50 per cent. of initial figure. In only one case was the uric acid reduced to a level below the mean for normal persons. It should be noted that the initial uric acid levels of patients in Table II was somewhat higher than that of those in Table I (mean 8·35 and 7·5 mg./100 ml. respectively).

During both salicylate and probenecid therapy, the serum uric acid was maintained at an average of 50·2 and 67·9 per cent. of the initial levels respectively (observed difference = 2·64 × standard error).

Four patients (Cases 8, 11, 15, 19) received continuous salicylate and probenecid therapy at different times. Table III shows the changes in serum uric acid levels during each of the two forms of treatment. In each case, salicylate (sodium salicylate in Cases 8, 11, 15, and aspirin in Case 19) effected an appreciably greater lowering of the serum uric acid level than did probenecid.

The effects of prolonged salicylate therapy are illustrated in Figs 2 and 3 (Cases 2 and 4). It is obvious that any defect in co-operation of

Table II

SERUM URIC ACID LEVELS IN SIX PATIENTS WITH CHRONIC GOUT BEFORE AND DURING PROBENECID THERAPY

Case No.	Duration of Therapy (months)	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)
		Initial			During Therapy			
		Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations	
11	19	10·6	35	2·12	7·1	28	1·32	66·0
(Fig. 4) 18	19	11·5	8	1·41	5·8	23	0·61	50·4
19	18	7·2	8	1·06	4·7	20	0·70	65·3
(Fig. 5) 15	15	5·0	9	0·50	3·1	17	0·41	62·8
20	13	9·1	27	1·68	6·7	11	1·81	73·6
21	12	6·7	10	1·38	6·0	14	1·11	89·2
Average	16							67·9

the patient will give rise to increased variability of the uric acid levels. The steady deterioration of salicylate in fluid form, together with the relative inaccuracy of measurement of fluid doses may explain the decreased variability of levels in Case 2 (Fig. 3) when the sodium salicylate was replaced by aspirin.

If frequent estimations of serum uric acid are performed at the start of salicylate therapy it is usually found that a maximal depression occurs within the first 3 weeks and that the uric acid is not maintained at this very low level. The lowest levels recorded in Case 4 (Fig. 2) were 0·8 and 0·9 mg./100 ml. on the third and sixth days respectively,

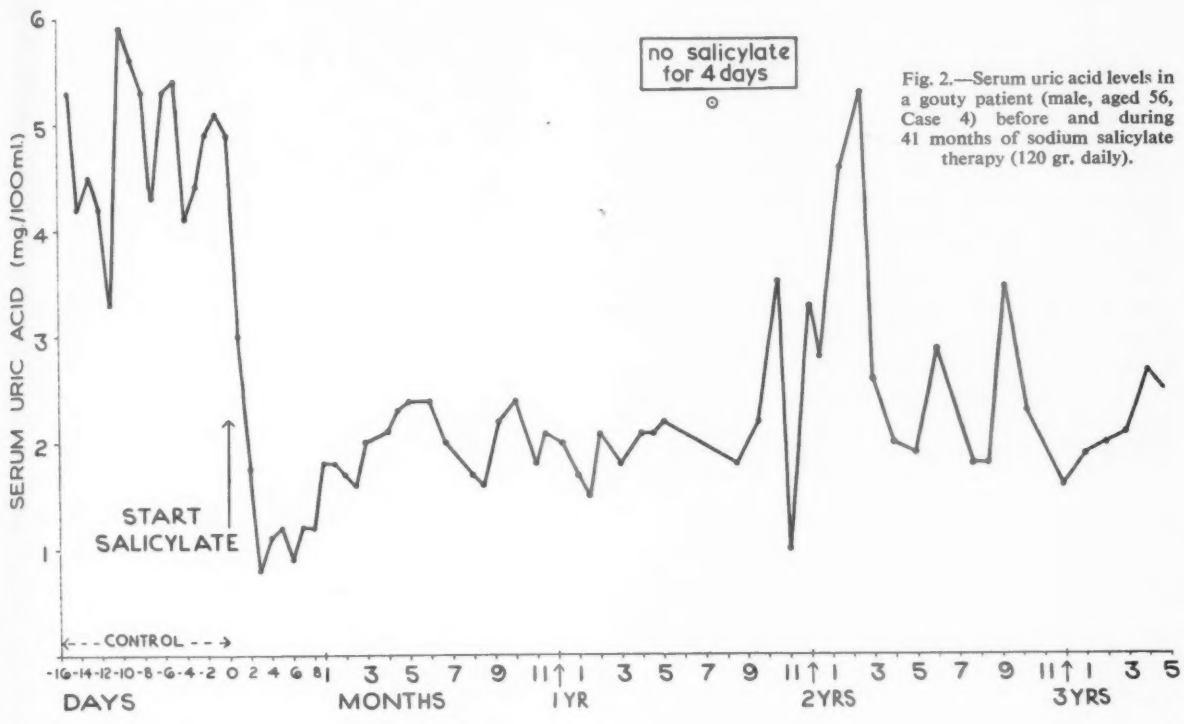

Fig. 2.—Serum uric acid levels in a gouty patient (male, aged 56, Case 4) before and during 41 months of sodium salicylate therapy (120 gr. daily).

TABLE III

SERUM URIC ACID LEVELS IN FOUR PATIENTS WITH CHRONIC GOUT BEFORE AND DURING SALICYLATE AND PROBENECID THERAPY

Case No.	Duration of Therapy (months)	Drug	Mean Serum Uric Acid (mg./100 ml.)						Maintained Serum Uric Acid (per cent. of initial level)
			Initial			During Therapy			
			Mean	Number of Observations	Standard Deviations of Observations	Mean	Number of Observations	Standard Deviations of Observations	
(Fig. 6) 8	27	Sod. Sal.	8·6	14	1·41	3·3	34	0·81	38·4
	3	Probenecid	—	—	—	4·8	3	0·30	55·9
(Fig. 5) 15	12	Sod. Sal.	5·0	9	0·50	1·8	15	0·31	36·1
	15	Probenecid	—	—	—	3·1	17	0·41	62·8
19	3	Aspirin	7·2	8	1·06	2·0	6	0·64	27·8
	18	Probenecid	—	—	—	4·7	20	0·70	65·3
11	18	Sod. Sal.	10·6	35	2·12	6·1	77	1·72	57·5
	19	Probenecid	—	—	—	7·1	28	1·32	66·0

The observed differences in uric acid levels during the two forms of therapy were 6·8 (Case 8), 10·2 (Case 15), 8·9 (Case 19), and 3·2 (Case 11) times the standard errors.

whereas the mean level during 41 months of treatment was 2·2 mg./100 ml. In Case 15 (Fig. 5), a level of 1·5 mg./100 ml. obtained on the seventh day, was, with one exception, the lowest figure obtained during one year's treatment.

Probenecid, like salicylate, causes an early maximal depression of serum uric acid which is not maintained (Fig. 4, Case 18). The lowest level (3·9 mg./100 ml.) occurred on the seventh day, and the level then rose gradually during the next 3 months. The mean level during 19 months of treatment was 5·8 mg./100 ml.

Figs 5 and 6 illustrate graphically the relative effects of sodium salicylate and probenecid in lowering the serum uric acid level. In Fig. 5 (Case 15) every estimation of uric acid during salicylate therapy is seen to be lower than the lowest reading during probenecid administration. In Fig. 6 (Case 8) only two of the many uric acid estimations during sodium salicylate therapy were higher than the three estimations made during probenecid therapy.

Table IV shows the results of experiments on Cases I-IV, four additional subjects, not included in the series of 21, designed to compare the uricosuric effects of single doses of sodium salicylate and probenecid, given either separately or together, during the 6 hours after administration. 100 gr. sodium salicylate induced an appreciably greater uricosuric effect that 2 or 4 g. probenecid in all phases of the test (Fig. 7). This was such that after the first 2 hours the uricosuric effect of salicylate was

TABLE IV

URINARY URIC ACID : CREATININE RATIOS

in four patients during the 6 hours following the control period (C), 100 gr. sodium salicylate (S), 2 g. probenecid (P_2), 100 gr. sodium salicylate with 2 g. probenecid ($S+P_2$), and 4 g. probenecid (P_4).

Case	Drug	Urinary Uric Acid : Creatinine Ratio (percentage of initial level)			
		Initial	During Therapy		
		−2-0 hrs	0-2 hrs	2-4 hrs	4-6 hrs
(*e*)	C	100	103	94·5	79
(*a*)	S	—	330	485	446
I (*b*)	P_2	—	263	251	264
(*d*)	$S+P_2$	—	339	392	411
(*c*)	P_4	—	246	324	280
	C	100	99	95	93
	S	—	282	353	270
II	P_2	—	237	248	164
	$S+P_2$	—	137	258	272
	P_4	—	140	263	284
	C	100	71	78	57
	S	—	400	375	332
III	P_2	—	258	273	231
	$S+P_2$	—	214	243	242
	C	100	92·5	102	69
	S	—	237	336	302
IV	P_2	—	248	202	164
	$S+P_2$	—	230	220	212

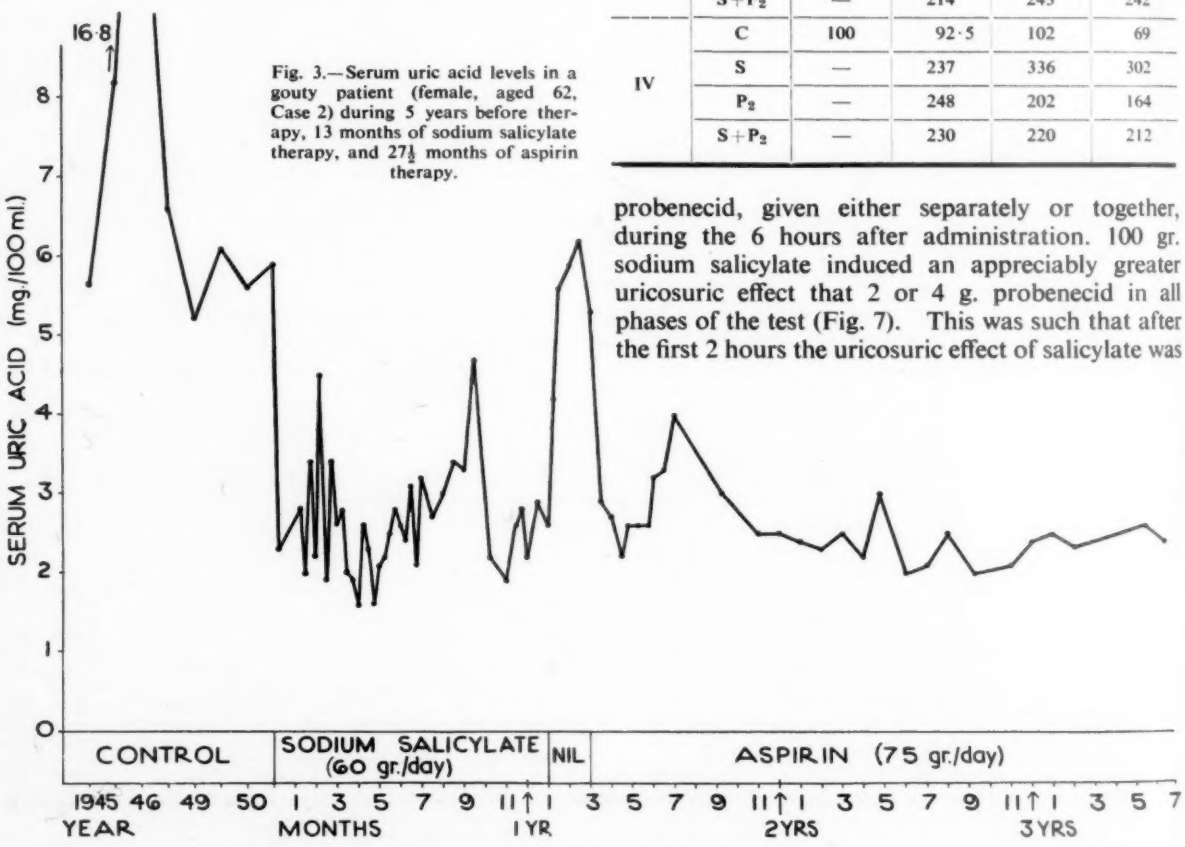

Fig. 3.—Serum uric acid levels in a gouty patient (female, aged 62, Case 2) during 5 years before therapy, 13 months of sodium salicylate therapy, and 27½ months of aspirin therapy.

double that induced by 2 g. probenecid. When the two drugs were given together the uricosuric effect was roughly comparable with that obtained by 2 g. probenecid alone.

Table V shows serum salicylate levels in Cases A-F, six additional subjects (four with rheumatoid arthritis and two with gout) after the oral administration of 100 gr. sodium salicylate.

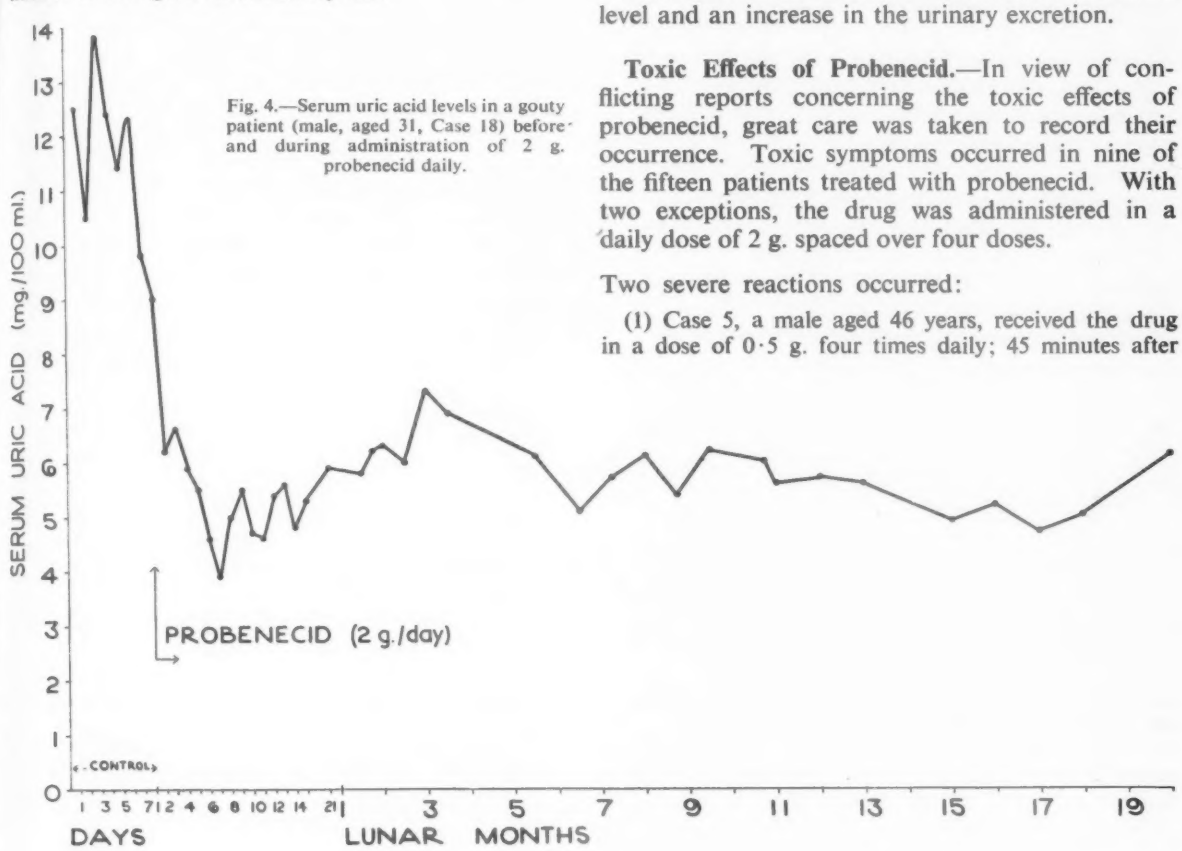

Fig. 4.—Serum uric acid levels in a gouty patient (male, aged 31, Case 18) before and during administration of 2 g. probenecid daily.

Fig. 8 shows serum and urinary uric acid levels in Case X, a gouty subject (not one of the series), before treatment, during administration of 90 gr. sodium salicylate daily, and later during additional administration of 2 g. probenecid daily. The addition of probenecid had no significant effect upon the uric acid levels and the combination of the two drugs continued to effect a marked reduction in the serum level and an increase in the urinary excretion.

Toxic Effects of Probenecid.—In view of conflicting reports concerning the toxic effects of probenecid, great care was taken to record their occurrence. Toxic symptoms occurred in nine of the fifteen patients treated with probenecid. With two exceptions, the drug was administered in a daily dose of 2 g. spaced over four doses.

Two severe reactions occurred:

(1) Case 5, a male aged 46 years, received the drug in a dose of 0·5 g. four times daily; 45 minutes after

TABLE V

SERUM SALICYLATE LEVELS IN SIX PATIENTS DURING THE NINE HOURS AFTER ORAL ADMINISTRATION OF 100 gr. SODIUM SALICYLATE IN 10 oz. WATER.

Patients received 10 oz. milk 2 hrs before start of test, and at 2nd, 4th, 6th, and 8th hours of test.

Diagnosis	Patient	Weight (lb.)	Serum Salicylate (mg./100 ml.)								
			0 hrs	¼ hr	½ hr	1 hr	2 hrs	4 hrs	6 hrs	8 hrs	9 hrs
Rheumatoid Arthritis ..	A	116	—	23·8	32·7	43·7	37·0	28·2	21·3	18·1	17·9
	B	147	—	28·4	31·9	44·1	39·6	30·5	25·8	22·9	21·0
	C	105	—	24·5	27·3	35·3	34·9	30·9	28·5	25·3	24·3
	D	221	—	14·7	17·8	23·9	26·7	24·3	23·0	20·8	19·8
Gout	E	202	—	14·5	16·6	28·1	28·1	23·5	18·2	17·4	14·6
	F	168	—	24·0	34·2	35·3	37·0	33·9	30·8	27·0	26·7
Mean		159·8	—	21·65	26·75	36·07	33·88	28·81	24·6	21·91	20·71

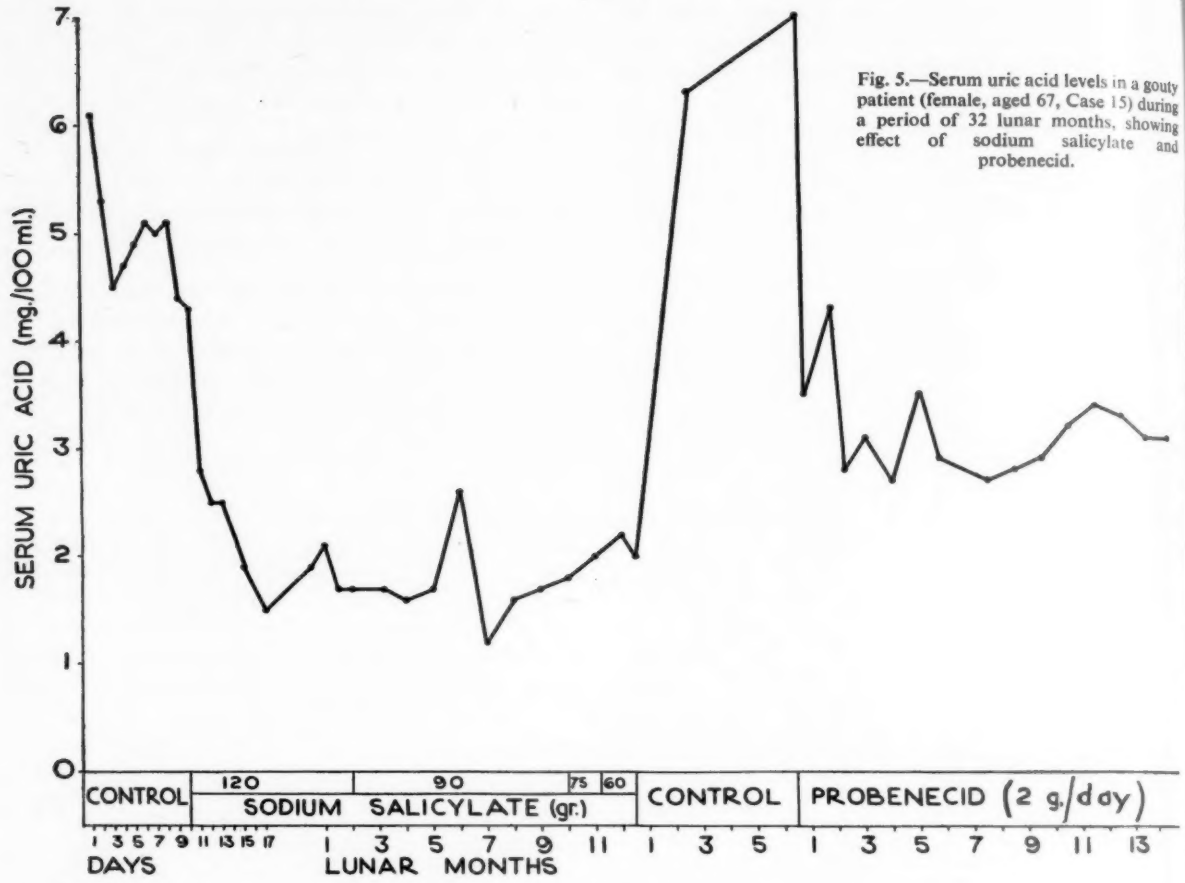

Fig. 5.—Serum uric acid levels in a gouty patient (female, aged 67, Case 15) during a period of 32 lunar months, showing effect of sodium salicylate and probenecid.

taking the fourth tablet, he felt hot, perspired profusely, and had a slight headache, but felt fit again after 2 hrs. He took a further tablet some 6 hrs later and had a return of symptoms which were more severe but again disappeared after 2 hrs. A further tablet was taken after another 6 hrs and once more he perspired and felt hot 45 minutes later, but his headache became intense and he lost consciousness for 10 minutes. Further therapy was stopped and the untoward symptoms disappeared within 18 hrs.

(2) Case Y, a male aged 50 years, received 0·5 g. probenecid three times daily. On the tenth day of treatment he developed a generalized maculo-papular rash with intense irritation, sore throat, and malaise. The temperature was 102° F. and the pulse rate 140. Further probenecid was stopped and the symptoms disappeared within 3 days. Six days later 0·5 g. probenecid was administered together with phenergan. Within 6 hrs the patient developed very severe malaise, with a return of the rash and sore throat. His temperature reached 104° F. and the pulse rate was 160 and irregular. For the next 24 hrs the patient's condition caused considerable anxiety to his general practitioner. Further probenecid was stopped; the rash disappeared after 2 days but the malaise persisted for a further 3 days.

Six patients suffered gastro-intestinal symptoms:

(1) Case P. Female, aged 49 years, anorexia, nausea, and vomiting developed on the second day of treatment. The symptoms persisted for a week and disappeared within 36 hrs of stopping further therapy.

(2) Case Q. Male, aged 45 years, epigastric discomfort and flatulence occurred from the second to fourteenth day, after which he became symptom-free. He was normally singularly free from alimentary symptoms and firm persuasion was necessary to get him to continue taking the drug.

(3) Case 8. Male, aged 51 years, anorexia and nausea occurred on the second day and vomiting on the third. Probenecid was stopped and no further symptoms occurred on recommencing the drug 2 months later.

(4) Case R. Male, aged 51 years, heartburn and a cramp-like pain across the upper abdomen occurred on the fourteenth day. The symptoms were fairly severe for a few days but gradually disappeared during the next 3 weeks.

(5) Case S. Male, aged 44 years, anorexia and nausea occurred from the third to seventh day of therapy.

(6) Case T. Male, aged 60 years, received probenecid for several months. Although he could tolerate 1·5 g. daily, raising the dose to 2 g. constantly induced heartburn.

One further patient, a male aged 29 years (Case 20), complained of pain in the left loin on the second day of treatment. The pain became severe and after 4 days the probenecid was stopped. The pain disappeared on the following day and did not recur when probenecid was restarted a week later. No other cause for the pain being found, it was assumed to be a result of probenecid administration.

Discussion

Chronic gout results from progressive deposition of urate in joint structures with ensuing tissue destruction, together with chronic inflammatory changes. Since 1950 it has been found possible to effect an appreciable and continued reduction in serum uric acid concentration to levels at which further precipitation of urate does not occur.

This measure might be expected to prevent further deterioration in the patient's condition and there is now ample evidence to confirm this. Furthermore, considerable solution and disappearance of urate deposits can be obtained, and this is usually accompanied by progressive improvement and later complete alleviation of the symptoms of chronic gout. It is likely that the rate and extent of urate reabsorption are related to the level of uric acid in the tissue fluid, and that so long as chronic symptoms persist the serum uric acid should be maintained at the lowest possible level. Once all chronic symptoms have resolved, it is no longer so essential to reduce the uric acid to the minimum, provided the level does not exceed that at which further deposition of urate could occur. This desired effect is obtained by the continued administration of drugs which have an effect on tubular cells whereby the reabsorption of uric acid is decreased, renal clearance increased, and the serum level reduced. Caronamide was the first such drug to be administered, but is no longer used,

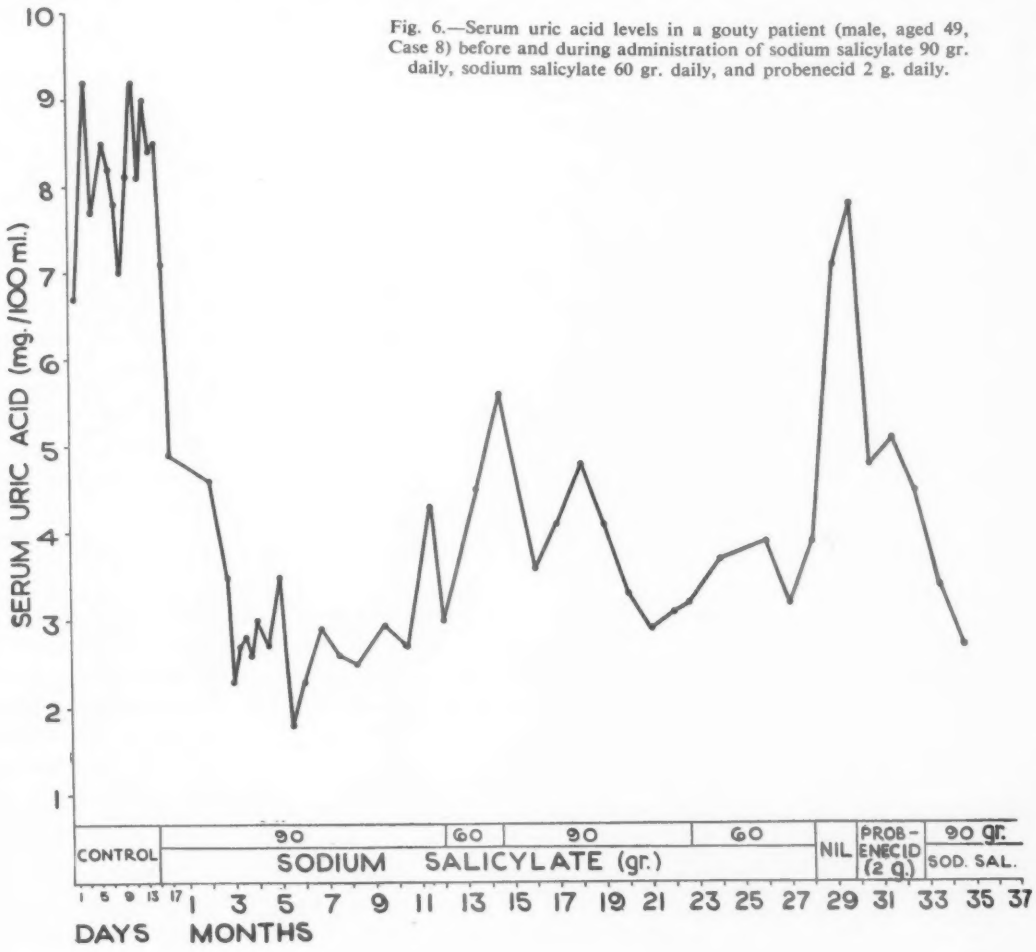

Fig. 6.—Serum uric acid levels in a gouty patient (male, aged 49, Case 8) before and during administration of sodium salicylate 90 gr. daily, sodium salicylate 60 gr. daily, and probenecid 2 g. daily.

and the present choice lies between probenecid and salicylate, the latter in the form of sodium salicylate or aspirin.

Probenecid is administered in tablet form, the normal dose being 0·5 g. four times daily. A larger dose usually produces gastro-intestinal symptoms, and a smaller dose is less effective. Various reports have indicated that the serum uric acid is reduced to approximately 50-70 per cent. of initial levels, but no attempt has been made to compare these changes with those obtained by salicylates, and little account has been taken of the fact that a maximum fall in serum uric acid usually occurs within the first few days of therapy and thus gives an exaggerated impression of the action of the drug (see Figs 2, 4, and 5). The latter fact applies equally to salicylate medication, and in presenting the results with the two drugs (Tables I-III) no account has been taken of the uric acid estimations during the first 3 weeks of treatment. Furthermore, critical assessment of published results on uric acid depression with either drug is impossible unless clear mention has been made of the period of therapy during which the uric acid was estimated. The present work has shown that in a series of seventeen patients receiving salicylate for periods of 9-45 months, the uric acid was maintained at a mean of 50 per cent. of the initial level (Table I), and that in a series of six patients receiving probenecid for periods of 12-19 months, the uric acid was maintained at a mean of 68 per cent. of the initial level (Table II). These changes were such that the uric acid was maintained at a mean level below that for normal persons in thirteen of the seventeen patients receiving salicylate, and in one of the six patients receiving probenecid. The results suggest that salicylate has an appreciably greater effect in lowering the serum uric acid than probenecid. In view of the drugs having been administered to two different series of patients, it was decided to give both drugs at different times to four other patients (Table III, and Figs 5 and 6). In each case salicylate had a significantly greater effect than did probenecid.

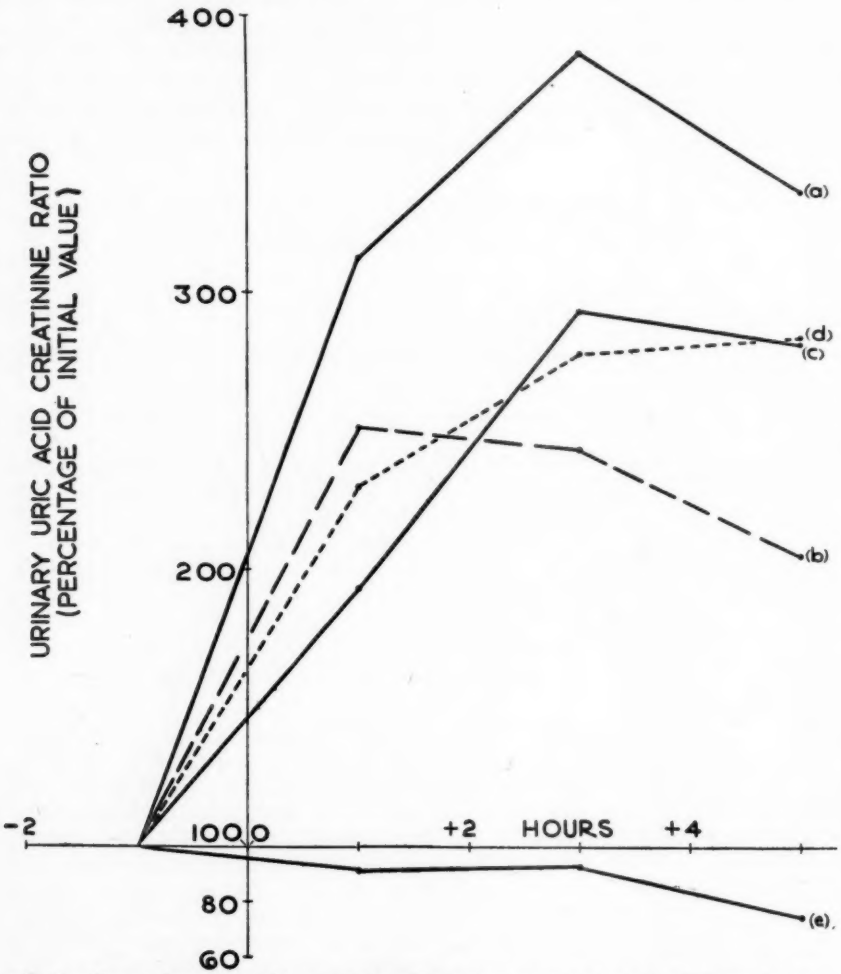

Fig. 7.—Mean urinary uric acid : creatinine ratios in four patients after oral administration of:
(*a*) 100 gr. sodium salicylate
(*b*) 2 g. probenecid
(*c*) 4 g. probenecid (two patients only)
(*d*) 100 gr. sodium salicylate + 2 g. probenecid
(*e*) control period.
(Results charted at middle of 2-hr periods.)

Further assessment of the relative effects of the two drugs was obtained by comparing the changes in the urinary uric acid : creatinine ratio during the 6 hours following the administration of 100 gr. sodium salicylate and 2 g. probenecid. The uricosuric effect of the salicylate was found to be approximately double that of the probenecid.

Both drugs are absorbed rapidly and give peak

concentrations within 2 hours of ingestion. The salicylate dosage provides a level of serum salicylate throughout the test which approximates to that obtained by the continuous administration of 30 gr. thrice daily. A single dose of 2 g. probenecid produces a level approaching 20 mg./100 ml. after 2 hours not falling below 5 mg./100 ml. within 8 hours, whereas the continued administration of 0·5 g. every 6 hours maintains a plasma concentration of between 2-6 mg./100 ml. (Boger and others, 1950).

Previous reports have stated that the coincident administration of probenecid and salicylates nullifies the uricosuric effect (Pascale and others, 1952; Gutman and Yü, 1952). The present work conflicts with this finding, for when single doses of the two drugs were combined an appreciable uricosuric effect occurred which was comparable with that obtained

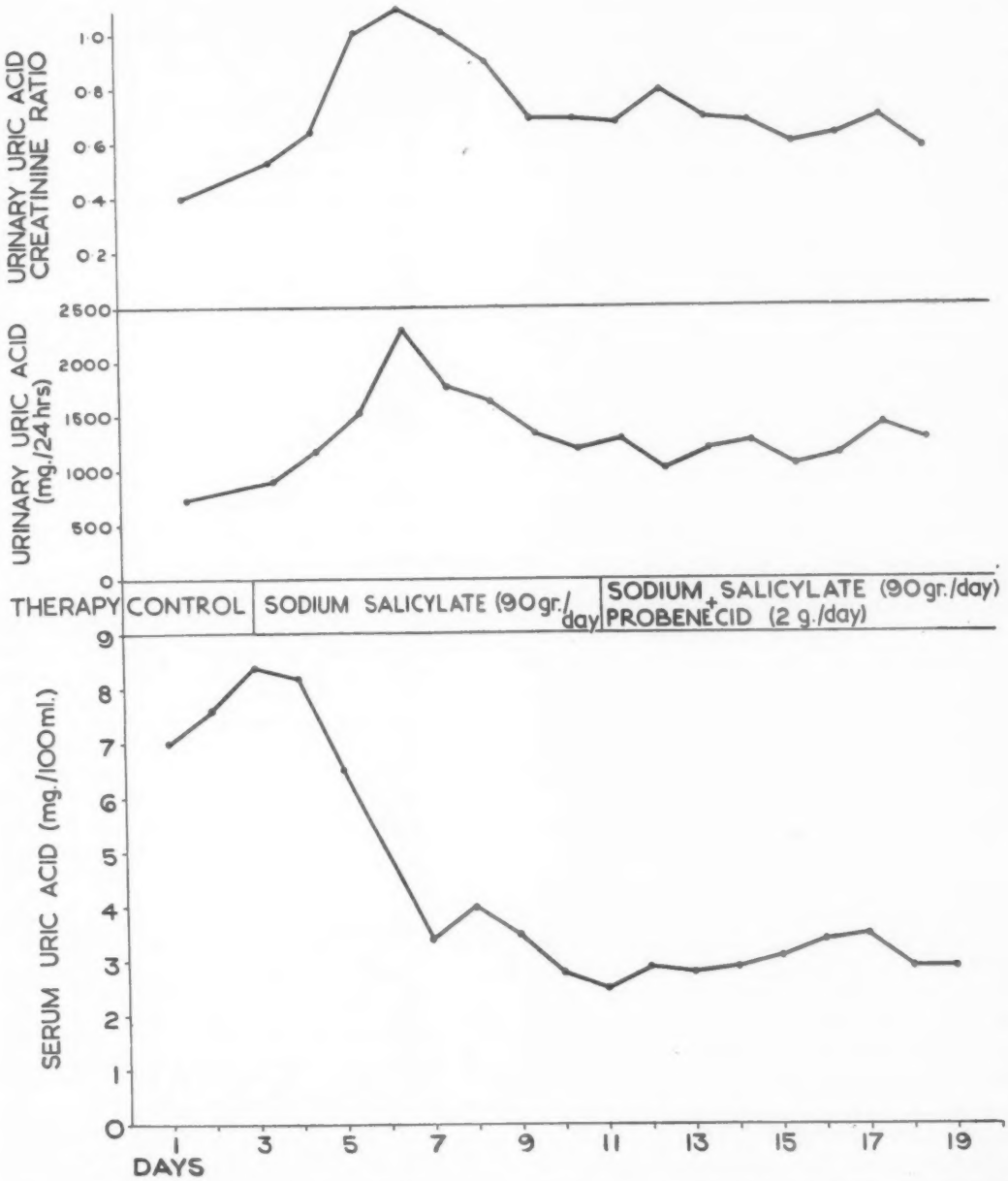

Fig. 8.—Effect of sodium salicylate alone and combined with probenecid on serum and urinary uric acid levels and urinary uric acid : creatinine ratio in a gouty patient (male, aged 42, Case X).

by probenecid alone. Furthermore, in a patient in whom the serum uric acid was maintained at a low level with continued salicylate therapy, the addition of probenecid failed to alter the uric acid concentration.

It appears, therefore, that with the exception of the few cases who cannot tolerate it in sufficient dosage, salicylate is likely to be more effective than probenecid in obtaining rapid relief of chronic symptoms. Chronic gout is a hopeless condition unless properly treated and patients should have every opportunity of obtaining full therapeutic relief. If facilities for close study are not available, it is probably more satisfactory to commence treatment with probenecid. In this event, however, if full relief is not obtained within a few months, the patient should not be regarded as incurable until salicylate therapy has been given a proper trial.

Allergic reactions to probenecid occurred in two of forty cases treated by Gutman and Yü (1952). Two of the present series of fifteen patients suffered severe sensitivity reactions to probenecid. Six patients suffered gastro-intestinal symptoms at the onset of treatment, but these disappeared with continued therapy.

The toxic effects of continuous salicylate therapy have been discussed previously (Marson, 1953a); further experience has amplified the earlier finding that, after the first few weeks, the large majority of patients tolerate the required dosage of salicylate (usually 90 gr. daily) with either complete freedom from salicylism or occasional and mild tinnitus and deafness. At the start of treatment it is useful to have the patients in hospital so that the salicylate dosage can be regulated to minimize the early toxic symptoms. In only five of forty patients have toxic symptoms been sufficiently severe to prevent continuous therapy in a dosage sufficient to maintain an appreciable lowering of the serum uric acid levels.

One difficulty with sodium salicylate therapy is the unpleasant taste of this drug in liquid form, but this can be avoided by dispensing it in capsules. Another disadvantage is the development of increased deafness in those already partially deaf; in such cases probenecid is to be preferred.

It is important to stress that, with the exception of those patients with impaired renal function, continued administration of salicylate or probenecid will effect a cure in most cases of chronic gout.

Summary

(1) An attempt has been made to compare the effects of salicylate and probenecid in lowering the serum uric acid of gouty patients.

(2) A maximum fall in serum uric acid levels occurs within a few days of commencing salicylate or probenecid. This is not maintained and gives an exaggerated impression of the effects of either drug during prolonged therapy.

(3) Seventeen chronic gouty patients received continuous salicylate therapy for 9-45 months. The mean level of serum uric acid was 50 per cent. of the initial level, and in thirteen of the seventeen patients the uric acid was maintained below the normal mean level in healthy subjects.

(4) Six chronic gouty patients received probenecid for 12-19 months. The mean level of serum uric acid was 68 per cent. of initial level, and in one of the six patients the uric acid was maintained at lower than the normal mean level.

(5) Four patients received salicylate and probenecid at different periods. In each case salicylate had a greater depressant effect on the serum uric acid level.

(6) Single doses of 100 gr. (6·5 g.) sodium salicylate had approximately double the uricosuric effect of single doses of 2 g. probenecid during the 6 hours following administration of the drugs.

(7) The coincident administration of probenecid and salicylates did not nullify the uricosuric effect.

(8) Toxic symptoms occurred in nine of the fifteen patients receiving probenecid. A rapid tolerance usually developed, but two severe reactions were encountered which necessitated withdrawal of the drug.

The long-term investigations have been facilitated by the development of a Gout Clinic in the Department of Therapeutics at the General Hospital, Birmingham. I am indebted to Professor A. P. Thomson for permitting this clinic to be set up, to various consultants of the United Birmingham Hospitals for referring patients, and to Dr. R. Gaddie and his assistants for the biochemical investigations. Further work has been carried out in Leeds, and I am grateful to Mr. F. J. N. Powell and Dr. J. Darnborough for the biochemical investigations. My thanks are due to Professor R. E. Tunbridge for assistance in the preparation of this article.

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Salicylate de soude et *probenecid* (Benemid) dans le traitement de la goutte chronique—l'évaluation de leurs effets relatifs sur la baisse du taux sérique d'acide

RÉSUMÉ

(1) On a tenté de comparer l'effet réducteur du salicylate de soude et du *probenecid* sur l'acide urique sanguin des goutteux.

(2) La plus grande chute du taux d'acide urique sanguin se produisit au bout de quelques jours de traitement par le salicylate ou le *probenecid*. Cette chute, capable de créer une opinion exagérée sur les effets de ces substances, ne se maintient pas au cours du traitement prolongé.

(3) Dix-sept goutteux chroniques furent soumis au traitement salicylique continu pendant 9 à 54 mois. Le chiffre moyen d'acide urique sanguin fut 50 pour-cent du chiffre initial et chez 13 malades sur 17 il fut en dessous de la moyenne pour des sujets normaux.

(4) Six goutteux chroniques furent soumis au *probenecid* pendant 12 à 19 mois. Le chiffre moyen d'acide urique sanguin fut 68 pour-cent du chiffre initial et chez un malade sur six il fut en dessous de la moyenne normale.

(5) Quatre malades furent traités par le salicylate et par le *probenecid* pendant de différentes périodes. Dans tous les cas l'effet réducteur du salicylate sur le taux sérique de l'acide urique fut plus prononcé.

(6) L'effet uricosurique d'une dose de 6,5 grammes de salicylate de soude fut deux fois plus grand que celui d'une dose de 2 grammes de *probenecid*, pendant six heures après l'administration de chaque médicament.

(7) L'administration simultanée de *probenecid* et de salicylates n'annulait pas l'effet uricosurique.

(8) Des symptômes toxiques se sont présentés chez neuf sur quinze malades au *probenecid*. Généralement une tolérance apparaissait vite mais on s'est heurté à deux réactions graves demandant la suppression du médicament.

Salicilato de sodio y *probenecid* (Benemid) en el tratamiento de la gota crónica—valoración de sus efectos relativos sobre la baja de la cifra sérica de ácido

SUMARIO

(1) Se ha tratado de comparar la acción reductiva del salicilato de sodio y del *probenecid* sobre el ácido úrico sanguíneo de los gotosos.

(2) La mayor caída de la cifra de ácido úrico sanguíneo ocurrió pocos días después de empezar el tratamiento con el salicilato o el *probenecid*. Esta caída, susceptible de crear una opinión exagerada respecto a los efectos de estos medicamentos, no se mantuvo con prolongar el tratamiento.

(3) Diecisiete gotosos crónicos fueron tratados sin interrupción con salicilatos durante 9 a 54 meses. La cifra media de ácido úrico sanguíneo fué el 50 por ciento de la cifra inicial y en 13 de los 17 enfermos no alcanzó la media para sujetos normales.

(4) Seis gotosos crónicos fueron tratados con *probenecid* durante 12 a 19 meses. La cifra media de ácido úrico sanguíneo fué el 68 por ciento de la cifra inicial y en uno de ellos no alcanzó la media normal.

(5) Cuatro enfermos recibieron el salicilato y el *probenecid* durante varios períodos. En todos los casos el efecto reductivo del salicilato sobre la tasa sérica del ácido úrico fué más pronunciado.

(6) Durante las seis horas después de su administración, el efecto uricosúrico de una dosis de 6,5 gramos de salicilato de sodio fué dos veces mayor que él de una dosis de 2 gramos de *probenecid*.

(7) La administración simultánea de *probenecid* y de salicilato no anulaba el efecto uricosúrico.

(8) Síntomas tóxicos presentáronse en nueve do los quince enfermos tratados con *probenecid*. Por lo general, una tolerancia solía establecerse rapidamente pero en dos casos hubo una reacción grave necesitando la cesación del medicamento.

ANATOMICAL CONSIDERATIONS IN INJECTION OF THE HIP JOINT

BY

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Recent developments in the treatment of affections of the hip joint by local injection of hydrocortisone, etc., require a safe and reliable route for injection. The methods described by Lanz and Wachsmuth (1938) comprise a lateral and a ventral approach to the joint. By the first method, the needle is pushed through the insertion of the gluteus medius muscle, the greater trochanter serving as the only landmark. The leg should be kept slightly adducted and the needle should pass right over the top of the greater trochanter in a horizontal direction, either in the frontal plane or with a slight dorsal deviation. By the second method, the needle is inserted over the femoral head and directed dorsally, and there are reliable landmarks to ensure correct positioning. By both methods the needle will enter the joint-space perpendicularly, so that only the point enters the actual cavity and the opening of the needle remains within the capsular layers. Such methods are only generally applicable in cases of exsudated joints, when the joint cavity has become filled with liquid and an exact approach is not necessary. An injection into an exsudated joint can be checked by the flowing out of the liquid, but in other cases there is no immediate response when the needle pierces the capsule. One must then be absolutely sure of the anatomical position of the needle.

Mawson (1946) described two methods of injecting joints in which there is no swelling:

(*i*) *Anterior.*—The needle is inserted midway between the great trochanter and the intersection of the femoral artery with Poupart's ligament; it is directed upwards, parallel with the femoral neck, inwards, and backwards.

(*ii*) *Posterior.*—The needle is inserted at a point just posterior to the great trochanter, and in an upward, inward, and forward direction.

This description seems to indicate that Mawson's approach to the joint cavity is tangential. The site of the needle is checked by injecting some fluid:

> Once inside the joint the solution will run in easily. If much pressure is necessary the needle is probably outside the joint cavity embedded in the fibres of the capsule.

Hollander, Brown, Jessar, and Brown (1951), dealing with the intra-articular use of cortisone and hydrocortisone, do not describe their method of injection. Kron (1948) recognized the difficulties of an intra-articular injection into the hip.

Oest (1950), dealing with this problem, indicated the only reliable route for injecting into a non-distended hip joint, *i.e.* the caudo-lateral approach, which ultimately leads the needle into the synovial sheath of the anterior aspect of the femoral neck. Oest guides the needle by means of metal threads, which have been stuck on the skin in the direction of the collum femoris. An *x*-ray photograph of the joint concerned shows the position of the femoral neck, and a second one taken after applying the metal threads serves as a control. This procedure is too laborious for routine use.

Technique

The method of injection should meet the following demands:

(*a*) it should be easy to perform so as to be practicable in general practice or in out-patient departments;

(*b*) the route of injection should be clear of large blood vessels or nerves;

(*c*) if possible, the injection should not be confined to a single narrow route, but should be practicable within a fairly large area.

We will take as a starting point a completed injection, where the top of the needle lies within the capsular extension along the neck of the femur. Running from a caudo-lateral direction, the needle

will touch the caudal side of the femoral head the moment it reaches the intra-articular position. It should be noted that in the caudo-lateral approach to the capsule, apart from other advantages, the needle meets a check as soon as it has gained entrance into the capsule. Though it has been said to be possible to reach this space by guiding the needle in a ventrolateral-dorsomedial direction (Mawson, 1946), this route is difficult to trace through lack of reliable landmarks; apart from this the needle meets no resistance and may be run too far, possibly into one of the larger vessels.

In following the caudo-lateral route, the needle should perforate the skin at a point up to 5 cm. caudal of the base of the greater trochanter. The point should be located in the plane of the ventral aspect of the femoral neck. Palpation of the greater trochanter gives sufficient guide to the site of injection; from this point the needle should run close to the ventral side of the femoral neck towards a point on the central third of a line from the ventral cranial iliac spine to the pubic tubercle (Fig. 1). This allows for an arc of deviation of 10-20°. There is not merely one possible route, and it does not matter where precisely the needle gains entrance to the ventral capsular pocket, as long as it keeps its caudo-lateral, cranio-medial direction. Therefore a considerable latitude is allowed in performing this injection. Our data may be regarded as defining safe limits for a successful result, but it is absolutely necessary to go right over the ventral surface of the femoral neck.

Carrying out the injection on an intact preparation or on a patient, the needle will meet some typical resistances. After perforation of the skin, the first resistance is offered by the fascia lata. The needle will pass through the muscular tissue unhampered, to meet further resistance in the joint capsule. Having passed this barrier, as soon as it touches the bone, the needle's whole aperture will be within the joint cavity (Fig. 2). There is one other potential obstacle, *viz.* the intertrochanteric line; it will be recognizable at once by its short distance from the skin and by the fact that the needle will meet it

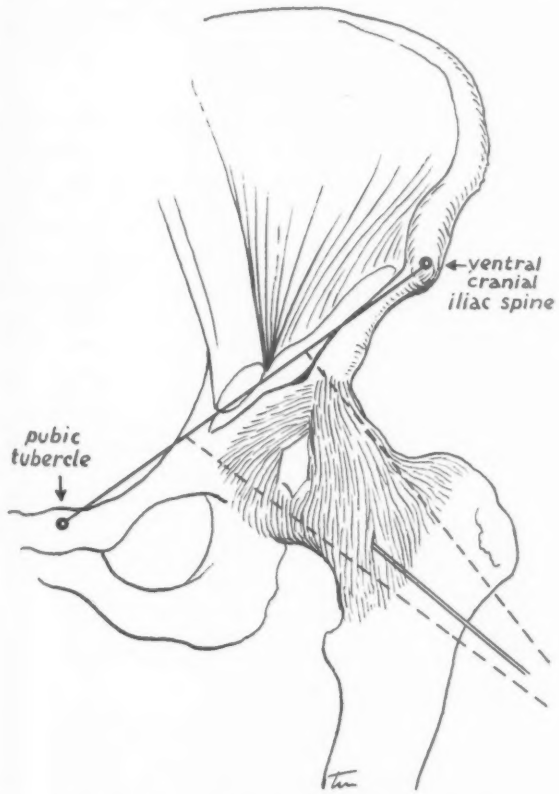

Fig. 1.—Drawing of a hip joint with the needle in the right position. Notice the site of perforation of the capsule and the direction of the route of injection in relation to the bony landmarks. The injection should take place within the dotted lines, which mark the "area of safety".

Fig. 2.—The capsule has been opened so as to show the position of the injection canal in relation to the femoral neck and synovial outpocketing at its ventral side. Both drawings are from a specimen injected with plastic material and then arranged as a joint preparation.

before passing the second "resistance". Should this occur, the needle should be withdrawn for a short distance, and then directed slightly ventrally of the first route.

We practised this injection on a great many cadaver subjects and found it always possible to run the needle into the joint cavity without difficulty.

Verification of Position

There is no real need to check the injection by other means than those already mentioned. If the needle is directed by means of the anatomical landmarks described above it cannot fail to enter the capsule. However, though it is not necessary to verify the position of the needle, its intra-articular position may be shown by various methods. The injection of an opaque material such as Ba-sulphate will show the site of injection on an *x*-ray film, since an intra-articular deposit of fluid will spread along and around the femoral neck. This method is applicable only to cadaver material. A fluid plastic substance may be injected into a cadaver joint cavity, and the injection may be continued while withdrawing the needle. After polymerizing the plastic substance the route of injection—a plastic thread—can be demonstrated in continuity with the joint cavity, and a plastic cast of the joint space may be made (Figs 1 and 2).

Injection

Finally, it is possible to inject a large quantity of fluid or air into the joint cavity, after which an increase of intracapsular tension will occur. When the piston-bar of the syringe is released, the fluid or air will run back into the syringe. We applied this method quite often to demonstrate the site of the tip of the needle. One of us tried this intervention on an apparently normal hip joint and found the liquid (a physiological salt solution) flowed back into the syringe. This phenomenon would not be seen in normal peri-articular tissue, for in normal tissue the liquid, when injected peri-articularly, spreads into the tissue spaces, and is not collected in one cavity. In pathological tissues one should be prepared to meet other reactions. Our observations seem to indicate that in certain circumstances, peri-articularly deposited fluid may flow back into the syringe. The tissue spaces seem to be occluded, by which procedure thick connective tissue plates will develop. This pathological tissue (Hartspann-Müller, "Myogelosen" Schade) does not absorb the fluid like a sponge, but opposes a fluid injection. Apparently the fluid collects, and is soon under high tension, so that releasing the piston-bar allows it to flow back into the syringe. *Evaluation of the reflow of fluid in pathological cases should therefore be made carefully and with much reserve.*

By appropriate handling of the needle failures may be entirely excluded. The touch of the needle against the caudal aspect of the femoral head provides instant proof of its position.

The method is easy to practise, there are no vulnerable arteries or nerves on its route, and the needle is guided by landmarks, a definite stop being formed by the femoral head itself.

We have found it almost impossible to penetrate the capsule on its lateral side, and we were not able in our cadaver experiments to inject air or liquid into the joint cavity by this route. It remains possible to reach and penetrate the capsule in its ventral aspect, approaching laterally from above. This method has notable disadvantages, since tracing is difficult and the needle meets no resistance the moment it pierces the capsule.

In our opinion this caudo-lateral approach in the direction of the femoral head, going close to the ventral aspect of the femur, should be chosen without reserve for all injections into non-distended hip joints.

Summary

The injection of a hip joint not containing a fluid reservoir presents various difficulties. For anatomical reasons the joint should be approached from the caudo-lateral side. The needle should be inserted at a point up to 5 cm. caudal of the base of the greater trochanter and should be directed to a point on the middle third of a line between the iliac spine and the pubic tubercle. The needle should run right over the ventral surface of the femoral neck. As soon as the needle touches a bony resistance—the caudal aspect of the femoral head—its aperture is within the joint space.

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Consideration anatomique de l'injection coxo-fémorale

RÉSUMÉ

L'injection de l'articulation coxo-fémorale amène des difficultés en cas où la capsule n'est pas distendue par une exsudation. Puisqu'il n'y a pas de réponse immédiate en perforant la capsule, il faut se confier entièrement aux points de repère anatomiques. L'aiguille doit être introduite à un point situé jusqu'à 5 cm. en-dessous du grand trochanter en direction médio-craniale, notamment vers un point du tiers moyen de la ligne épine iliaque antéro-supérieure—épine du pubis.

L'aiguille, cheminant au ras de la face ventrale du col du fémur, se heurtera contra la face inférieure de la tête. À ce moment l'aperture de l'aiguille aura une position intra-articulaire, à savoir dans le cul de sac capsulaire de la face ventrale du col du fémur.

Consideraciones anatómicas sobre inyecciones en la articulación de la cadera

SUMERIO

Una inyección en la articulación de la cadera que no contiene líquido presenta varias dificuldades. Por razones anatómicas habrá que acostarla caudo-lateralmente. Se inserta la aguja á 5 cm. debajo del gran trocanter en el sentido caudal y se la dirige hacia un punto situado sobre la media tercera parte de la línea entre la espina iliaca y la tuberosidad púbica. La aguja debe pasar directamente sobre la superficie ventral del femur. Al sentir con la aguja una resistancia ósea—el aspecto caudal de la cabeza femoral—se sabe que la punta está en el espacio articular.

EFFECT OF THYROIDECTOMY IN RHEUMATOID ARTHRITIS

BY

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There are numerous reports in the literature on the relation between different joint symptoms and thyroid function (*e.g.* Macalister, 1904; Jones, 1909; Moravicella, 1928; Swaim, 1929; Duncan, 1932; Nyfeldt, 1937). Thyroid medication can essentially alleviate the joint symptoms of hypothyrotic patients, as mentioned by Swaim (1929) and Nyfeldt (1937). Duncan (1932) and Traut (1952) observed that in hyperthyrosis symptoms of rheumatoid arthritis could be considerably improved by thyroidectomy. On the other hand, Traut (1952) claims to have observed the onset of typical symptoms of rheumatoid arthritis as a sequel to strumectomy in three patients.

The generally accepted opinion is that disturbed thyroid function has no aetiological significance in rheumatoid arthritis (Swaim, 1929; Pemberton, 1932; Bauer, 1939; Freyberg, 1942; Traut, 1952).

Finally it should be said that prodromal symptoms of rheumatoid arthritis and of thyrotoxicosis are extremely apt to cause confusion (Borman, 1945; Hollander, 1953).

Since the number of cases reported in the literature is small, and the problem of correlation between rheumatoid arthritis and strumectomy has been dealt with only superficially, we think it worth while to present the following material.

Methods

We have examined a series of patients suffering from rheumatoid arthritis in the year 1941, and found that 48 had been subjected to strumectomy. Twenty of them, who had been operated on quite a long time before the onset of rheumatoid arthritis, had been omitted from this series. The remaining 28 had been operated on either while suffering from rheumatoid arthritis, or immediately before its onset.

Assuming that any effect of strumectomy, either beneficial or harmful, on rheumatoid arthritis might be due to the surgical intervention *per se*, we also studied a control series. This consisted of 97 rheumatoid arthritis patients who had been subjected to major operations such as laparotomy or orthopaedic operations. This series did not include cases of removal of possible foci, nor operations affecting the endocrine system in any way.

The effect of operation on the course of rheumatoid arthritis is shown in Table I, which demonstrates a difference between the strumectomy series and the control series. A majority of the former exhibited aggravation of rheumatoid arthritis after operation. In seven cases a sudden onset of the disease occurred either immediately or approximately one month after strumectomy. We classified as marks of aggravation rapid involvement of new joints after the operation (fifteen cases), or a marked increase in the activity of the disease (three cases). In one case, this deterioration seemed to be of a transient nature, as remission took place approximately 6 months after the operation, but during this time he was given abundant doses of thyroid hormone. In no case was the post-operative course associated with fever.

TABLE I
POST-OPERATIVE COURSE OF RHEUMATOID ARTHRITIS

Cases	Total Cases	Post-operative Course of Disease			
		Unchanged	Improved	Worse	Onset
Strumectomy	28	8	2	18	(7)
Controls ..	97	80	9	8	(1)

Indications for the strumectomy are shown in Table II.

TABLE II
INDICATIONS FOR OPERATION IN THE STRUMECTOMY CASES

Effect on Rheumatoid Arthritis	No. of Cases	Principal Indication for Operating		
		Toxicosis	Pressure Symptoms	Toxicosis? A. rh. prodromes?
Unchanged	8	5	3	—
Improved	2	—	2	—
Aggravated	18	8	6	4
Onset	(7)	(2)	(1)	(4)

Results

(1) In this series not one case from the thyrotoxicosis group showed any marks of improvement in joint symptoms after the strumectomy. The only patients in whom improvement could be noted were those suffering from pressure symptoms.

(2) In those cases in which strumectomy had led to aggravation of rheumatoid arthritis, the surgical indication consisted of both toxicosis and pressure symptoms, but in four cases the indications had been so indefinite that it must be presumed that there had been some confusion between prodromal symptoms of rheumatoid arthritis and thyrotoxicosis.

In Finland particularly, there is a very high incidence of nodular goitre (*e.g.* Setälä, 1954), whilst rheumatoid arthritis is also a fairly common disease in this country. We have therefore every reason to stress the difficulties in the differential diagnosis of these two diseases, and to bear in mind that, under certain conditions, confusion can easily occur.

Summary

(1) In patients affected with rheumatoid arthritis, strumectomy frequently results in a marked aggravation of this disease, according to the assessment based on the present study. Since no such tendency could be noted in the controls, this aggravation must be considered a specific sequel, the effect of which is mostly manifested in the sphere of the endocrinal balance.

(2) It was obvious in some of the cases that there had been a failure to discriminate between prodromal symptoms of rheumatoid arthritis and symptoms of thyrotoxicosis.

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Effet de la thyroidectomie sur l'arthrite rhumatismale

RÉSUMÉ

(1) Chez des malades atteints d'arthrite rhumatismale la thyroidectomie est souvent suivie d'une aggravation prononcée de cette maladie, sans qu'on note une tendence semblable chez les témoins. On doit donc considérer cette aggravation comme séquelle spécifique dont l'effet se manifeste surtout dans le domaine de l'équilibre endocrinien.

(2) Il était évident que dans certains cas on a manqué de distinguer entre les prodromes de l'arthrite rhumatismale et les symptômes de la thyreotoxicose.

Efecto de la tiroidectomía sobre la artritis reumatoide

SUMARIO

(1) En enfermos con artritis reumatoide se observa a menudo una agravación pronunciada de esta enfermedad después de la tiroidectomía, sin que se note tal tendencia en testigos. Esta agravación debe considerarse como una consecuencia específica cuyo efecto se manifesta principalmente en el dominio del equilibrio endocrino.

(2) Fué evidente que en ciertos casos hubo falla de discriminar entre prodromos de la artritis reumatoide y síntomas de la tireotoxicosis.

BOOK REVIEWS

HOSPITAL REPORTS, 1953*

These reports from rheumatism units in three hospitals are all distinctly different in presentation, which may encourage those who feared that a National Health Service would stifle individual initiative, especially in research. The Taplow report, indeed, discusses this very problem, pointing out that most research is done either in the Universities or under the aegis of the M.R.C. (and in this case often with the help of the Empire Rheumatism Council), and describes the difficulties which had to be overcome in setting up and organizing a new special unit. Whilst all three reports reflect the different circumstances in which the departments grew up, only the Taplow report gives an account of these administrative aspects, perhaps because it is a quinquennial rather than an annual report.

Each unit appears to treat a different type of patient. At Taplow the primary concern is with rheumatic fever and Still's disease; these represent 128 and 50 respectively of 312 discharge diagnoses during 1952, whilst the West London and the Royal Free record no cases of rheumatic fever. On the other hand, at Taplow the diagnosis of osteo-arthritis or disk disorder does not appear whilst at the West London 37·6 per cent. of the out-patients had osteo-arthritis and 13·2 per cent. disk disorders, and at the Royal Free the proportions were 25 and 5 per cent. The West London is the only unit which records cases of gout in a separate category (1·6 per cent.).

Thus the three research programmes each have a different emphasis. Covering as it does a 5-year period, that at Taplow appears formidable and impressive—therapeutic trials of ACTH, cortisone, and salicylates in rheumatic fever and rheumatoid arthritis, cardiological studies, long-term follow-up studies with control groups, and experimental research into certain more fundamental aspects of connective tissue changes in these conditions. These are briefly described with a full bibliography for those who wish to read the published papers (seventy are listed).

The West London report, in addition, includes a few brief original papers, including experiences with long-term cortisone in rheumatoid arthritis, clinical trials with ACTH of varying batches, absorption and excretion of phenylbutazone, a clinical trial of a rubifacient, intra-articular cortisone and hydrocortisone, and two case histories of special interest.

The Royal Free report also gives a brief account of research work in progress on synovial fluid, intra-articular temperatures, serum protein changes in rheumatoid arthritis, pharmacological effects of phenylbutazone, joint clearance of radio-active sodium, intra-articular hydrocortisone, and experiences with long-term cortisone. There is also an analysis of the type of case admitted together with a continuation of the follow-up studies reported in previous years.

A valuable feature of this type of report is that it gives important background knowledge to those working in this field when reading papers published from these departments. The lack of such information often handicaps workers who have not had the opportunity of visiting departments overseas, and these reports will at least go some way towards meeting this problem for our foreign colleagues. They should also be helpful to those working on the planning side of the hospital services by showing the contribution such departments make towards solving the problems of disease, both in research and in dealing with the day-to-day practical problems of rheumatism in the community. R. M. MASON.

Copies of these reports are available free on application to the Physician in Charge:

West London Hospital Report: Dr. W. S. C. Copeman, Department of Rheumatic Diseases, West London Hospital, Hammersmith Road, London, W.6.

Canadian Red Cross Memorial Hospital Report: Dr. E. G. L. Bywaters, Canadian Red Cross Memorial Hospital, Taplow, near Maidenhead, Berks.

Royal Free Hospital Report: Dr. E. T. D. Fletcher, Department of Rheumatology, The Royal Free Hospital (North-Western Branch), Lawn Road, Hampstead, London, N.W.3.

Tratamiento de los Reumatismos. By J. Rotés-Querol. 1954. Pp. 188, 51 figs, bibl. Manuel Marín, Barcelona.

This small volume, which is essentially up to date, attempts a critical analysis of the recognized treatments of the commoner rheumatic disorders. Percentages of cure, or complications, with the different therapeutic agents are freely scattered through the pages and are usually derived from reputable sources. The material is well classified, so much so that the summaries at the end of each chapter are rather unnecessary. The 51 simple illustrations are decidedly helpful. It is surprising to hear the author mention gold as a valuable agent in ankylosing spondylitis; also his view that a prolapsed disk is a rare cause of cervico-brachial neuralgia is, to say the least, not universally accepted. Doubt has recently been thrown on the effect of Butazolidin in lowering blood uric acid levels. On the whole, however, this book is well balanced and one would not quarrel with most of its recommendations. It would be useful to have it handy when confronted with the problem of treating a case, and this is the author's prime intention.

PAUL B. WOOLLEY.

* Canadian Red Cross Memorial Hospital, Taplow. *Report of the Special Unit for the Study and Care of Juvenile Rheumatism.*
West London Hospital. *Department of Rheumatic Diseases.*
The Royal Free Hospital, London. *Department of Rheumatology.*

WORLD HEALTH ORGANIZATION

EXPERT COMMITTEE ON RHEUMATIC DISEASES, FIRST REPORT, 1954

Members of the Committee

DR. W. S. C. COPEMAN (*London*), Chairman.
PROF. F. COSTE (*Paris*).
PROF. G. EDSTRÖM (*Lund*).
PROF. J. GOSLINGS (*Leyden*), Rapporteur.
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DR. E. T. CONYBEARE (*London*).
DR. A. HÖJER (*Trivandrum*).
DR. J. S. PETERSON (*W.H.O.*).
DR. T. S. SZE (*W.H.O.*), Secretary.

W.H.O. Expert Committee on Rheumatic Diseases. First Report.* April, 1954. Wld Hlth Org. techn. Rep. Ser. No. 78. Published in English and French. Pp. 25. (25 *cts*; *Swiss frs* 1; 1*s.* 9*d.*)

Chronic rheumatic diseases have been somewhat neglected from both a medical and a research viewpoint, despite their social and economic significance as causes of long-term disability. At present there is lack of knowledge concerning the aetiology of this group of diseases, and treatment is therefore still largely palliative and prevention impossible.

A review from a public-health standpoint of the chronic rheumatic diseases of articular and non-articular types is presented in a recent Technical Report prepared by a W.H.O. expert committee on this subject. It is noted in the report that, as an international health problem, the rheumatic diseases must of necessity be considered less important in some countries than illnesses of an infective or parasitic nature which are amenable to specific measures of control.

Nomenclature and Classification

Both a nomenclature and a classification are needed for the group of diseases termed "rheumatic". The task of formulating a nomenclature has been undertaken by a special committee of the International League against Rheumatism. As for a classification, any which might be made would have to be considered provisional, since there are as yet too many unknowns in the aetiology and pathogenesis of rheumatic diseases.

The following general statement is made in the report:

"Rheumatic diseases affect the locomotor system, in which they are important causes of pain, dysfunction, and anatomical change. The most important link between them is now considered to be that they are all diseases peculiar to the connective tissue and that, as such, they all show reactions peculiar to this tissue and especially of its collagen element. It should be emphasized that, although the etiology of the different rheumatic diseases is probably extremely diverse, these connective tissue reactions are common to all of them; in this connexion it should be noted that not only connective tissue of the locomotor system, but also to some extent that of the viscera, the nervous system, the haematopoietic system, the skin, etc., may be affected by these diseases."

In an appendix to the report is a list of the diseases commonly accepted as rheumatic and of other diseases presenting rheumatic features.

Incidence and Prevalence

Existing data on the incidence and prevalence of chronic rheumatic diseases are not adequate for any of the purposes for which morbidity statistics are commonly used. Four methods have been used to obtain such data as do exist: notification, analysis of medical sickness records (such as health insurance forms), analysis of hospital records, and sickness surveys. Of these four, only the last is considered likely to yield data which would enable statisticians to make satisfactory studies of the chronic rheumatic diseases. To be really useful, such surveys would require considerable medical and technical organization, and the home-visiting would have to be done by doctors with special training and interest in the rheumatic diseases and with facilities available for making and checking diagnoses.

Uniformity in diagnostic headings would aid in making the data from such surveys comparable from country to country; and, for this purpose, the following are suggested in the report:

Rheumatic fever
Rheumatoid arthritis (and allied conditions such as ankylosing spondylitis, Still's disease, etc.)
Osteo-arthritis (arthrosis)—including the spine
Other forms of arthritis—infective and traumatic
Gout

* This review is reprinted from *Chron. Wld Hlth Org.*, **8**, 142.

Lesions of the intervertebral disks
Non-articular rheumatism ("fibrositis")—in various parts of the body
"Rheumatism" unspecified.

A summary of statistical studies which have been made in several countries during or since the Second World War is included in an appendix to the report. Though these studies are of limited value, they give some idea of the prevalence and incidence of the rheumatic diseases. For example, in a survey made of a "probability" sample of the population of the U.S.A. in 1951, the main conclusion reached was that there were about ten million persons over the age of 14 years (*i.e.*, about one-tenth of the total population over this age) who believed they were suffering from either "arthritis" or "rheumatism". It was estimated that about six million of these ten million persons had been told by a doctor that their complaints were due to one or another of these two conditions.

A study of rheumatic diseases as causes of disablement and of long- and short-term illnesses in relation to the social security arrangements of the metropolitan Paris area revealed that, in about 10 per cent. of 50,000 disabled persons, the cause of the disablement was a rheumatic disease, 40 per cent. of these 5,000 persons being disabled by the cardiac sequelae of rheumatic fever. About 6 per cent. of 50,000 cases of long-term illness (*i.e.*, longer than six months but less than three years) were also attributed to rheumatic diseases, excluding cardiopathies due to rheumatic fever.

In Sweden, an inquiry made in 1943 showed that during the year 2·5 per 1,000 of the population had sought medical care for rheumatoid arthritis; 1·7 per 1,000, for osteo-arthritis; and 4 per 1,000, for sciatica and fibrositis. The data also revealed that the total number of sufferers from rheumatic diseases (including rheumatic fever) that had received medical care was about 90,000. During the year, approximately 2,100 hospital beds were occupied by rheumatic patients, but it was estimated that the total number of beds needed for treatment of such patients was about 5,000, or at least seven per 10,000 of the population.

No definite conclusions about the aetiology and pathogenesis of rheumatic diseases can be drawn from the studies made thus far. However, certain generalities emerge concerning age and sex incidence: in rheumatoid arthritis, there is a higher incidence in the middle age-groups of the female sex than in the male; there are also differences in the sex incidence of osteo-arthritis, in which incidence appears to rise steadily with age; and some studies indicate that among men laborious occupations are associated with an earlier onset of some chronic diseases with rheumatic features (*e.g.*, lesions of the intervertebral disks) than is the case among the general population.

Prevention, Control, and Treatment

Specific preventive measures against the rheumatic diseases are as yet not feasible, except possibly against rheumatic fever, in which the streptococcal infection is probably an aetiological factor which might be countered by the use of antibiotics and of sulfonamides.

Early recognition and prompt treatment are very important. Treatment methods are largely empirical but may nevertheless yield good results. The most commonly used methods are general medical measures, including the administration of special drugs such as gold; physiotherapy; and orthopaedic techniques, including splinting, manipulation, and operative procedures. The report states that the use of active steroid and other hormones, which has recently been tried, can be of value in carefully selected cases, but must be considered as still largely in the experimental stage.

It is essential that adequate treatment facilities and hospital beds be made available for patients suffering from rheumatic diseases; that general practitioners be better informed concerning the management of rheumatic cases; that the services of specialists in these diseases be at the disposal of patients and of general practitioners; and that research on the rheumatic diseases be encouraged. Attention must also be given to limitation of disability, through patient education as well as therapeutic measures; to rehabilitation of those disabled by rheumatic diseases; and to health education of the public, which is needed to correct the erroneous belief that these diseases are incurable, practically untreatable, and usually disabling.

CORRIGENDUM

Volume 13, March issue, p. 74, in the list of officers of the Heberden Society:
For C. E. Fletcher please read E. T. D. Fletcher

HEBERDEN SOCIETY

Heberden Round.—This was held at the Littlewood Hall, General Infirmary, Leeds, on May 7, 1954. Professor S. J. Hartfall, who conducted the round, showed a series of cases illustrating various aspects of rheumatism.

Case 1, *Spondylosis with myelopathy and a neuropathic joint.*—A man aged 78 suffered from a painful and subsequently unstable and painless left knee; in addition he developed paraesthesiae, first in the left arm and then in the right.

Examination showed some limitation of the shoulder movements, with muscle wasting and an unstable left knee with pronounced quadriceps wasting. There was no sensory loss but bilateral ankle clonus was present with an extensor response on the left side. Myodil injection into the theca showed two breaks; one in the lumbar region at the level of L3-4 and the other in the cervical region between C4-5. In spite of the absence of sensory loss, the lesions seemed to be attributable to cord and nerve root compression, and Professor Hartfall used this patient to emphasize the title of the recent Heberden Oration: "Spondylosis, the known and the unknown".

Case 2, *Haemorrhage from gastric erosions after oral Butazolidin. Gastroscopy.*—A man aged 64 suffered from rheumatoid arthritis and had been treated with Butazolidin, which was followed by dyspepsia and melaena. On gastroscopy, multiple acute erosions of the gastric mucosa were seen.

Case 3, *Rehabilitation of a chronic rheumatoid cripple, terminated by fatal recurrence of oesophageal haemorrhages.*—A woman aged 54 had been a rheumatoid cripple who was remarkably rehabilitated by cortisone and physiotherapy, but while on the drug she developed dyspepsia and haemorrhage from a megaoesophagus. Ulceration of the oesophagus and pyaemia was found *post mortem*.

Case 4, *Rehabilitation of a chronic rheumatoid spondylosis with orthopaedic procedures and prolonged physiotherapeutic rehabilitation.*—A man aged 43 had rheumatoid spondylitis with severe involvement of the feet and hands, in addition to involvement of the spine. Treatment with cortisone, orthopaedic operation, and manipulation had produced considerable improvement and he could then walk with the aid of crutches.

Case 5, *A case of polyarthritis with neutropenia and splenomegaly. Felty's syndrome. ? for splenectomy.*—A woman aged 31 had rheumatoid arthritis with neutropenia and splenomegaly, commonly known as Felty's syndrome; the question of splenectomy was discussed.

Case 6, *Exophthalmic ophthalmoplegia treated with cortisone and ACTH. Development of ? thyrotoxic cirrhosis not related to therapy.*—A woman aged 58 had thyrotoxic ophthalmoplegia; she was treated with cortisone and ACTH and developed cirrhosis of the liver. This can occasionally occur in thyrotoxicosis, and was believed not to be related to the hormone therapy.

The following demonstrations were also on view:

G. H. ILLINGWORTH	New Radiological Techniques.
R. E. TUNBRIDGE, D. A. HALL, G. C. WOOD	Studies in Connective Tissue.
D. H. COLLINS ..	Pathology.
D. TAVERNER ..	Electromyography.
T. W. SUTHERLAND, S. J. HARTFALL	Pathology.

Short papers were given by the following speakers:

Dr. Derek Taverner: "The Relation of Electromyographic Changes to Somatic Pain". Since sustained muscular contraction is painful, it is possible that the pain of non-articular rheumatism may be due to muscular spasm. Dr. Taverner reviewed Elliot's observations in this connexion, but pointed out that several conditions in which the electromyographic abnormalities were similar to those noted by Elliot were, in fact, painless, for example, progressive muscular atrophy. In severe cramp the electromyographic activity recorded was much more intense and quite unlike what Elliot found in his cases. He illustrated the effect of cramp by a patient in whom knitting produced cramp of the right trapezius muscle. Dr. Taverner reviewed Frykholm's recent work, in which, when the ventral roots were exposed at operation and stimulated either by pinching or by heat, deep muscular pain was felt, and discussed the incompleteness of our present knowledge of pain mechanisms.

Dr. D. A. Hall: "The Electron Microscope Study of Collagen and Elastic Tissue". He pointed out that connective tissue consists of collagen and elastic tissue in various proportions, both of which are embedded in a highly polymerized polysaccharide matrix. The electron microscope shows the characteristic banding of collagen, whereas elastin is not banded. Illustrating the effects on connective tissue of various factors such as stretching and heating, he

emphasized that collagen and elastin should be considered together, stating that, owing to the limited nature of present knowledge and the differing behaviour of these tissues under differing circumstances, it is possible to draw mistaken conclusions from experimental work in this field.

**Dr. F. G. W. Marson:* "Comparative Study of the Efficacy of Prolonged and Continuous Treatment with Salicylate and Probenecid in lowering the Concentration of Serum Uric Acid in Chronic Gout".

A Clinical Meeting was held at the Royal Bath Hospital, Harrogate, on May 8, 1954.

Professor S. J. Hartfall described his experience with intermittent administration of corticotrophin by repeated slow intravenous infusion in 427 patients, including 331 cases of rheumatoid arthritis. Occasionally thrombosis of the vein used for the injection occurred, but the vein usually recanalized within 5-10 days. Functional capacity (assessed by a modification of the grading adopted by the American Rheumatism Association) improved in a proportion of cases, but the anatomical status of the disease was not influenced, except perhaps in its very early stages. Treatment sometimes produced a temporary regression of activity which facilitated physical therapy; it might also be useful as a prelude to a course of injections of gold, as a supplement to cortisone, and in occasional patients in whom long-acting corticotrophin proves ineffective. Acute cases of "frozen shoulder" sometimes improved dramatically, and the treatment was worth considering in cases of osteo-arthritis with effusions or acutely painful episodes.

In the discussion of this paper doubt was cast on whether the improvement rate exceeded the "inevitable 70 per cent.", and attention was drawn to the danger of allowing premature weight-bearing when symptoms had been suppressed by cortisone or corticotrophin.

Dr. J. M. Bremner described a patient with rheumatoid polyarthritis, in whom one knee was more severely affected than any other joint. It was decided to inject this knee with hydrocortisone intra-articularly, and two injections of 25 mg. were given into this knee at weekly intervals. When a further injection was given 2 weeks later the fluid was found to contain tubercle bacilli and at operation an acute tuberculous arthritis of the knee was found. Dr. Bremner emphasized the possibility of tuberculous involvement of a joint in a patient who appeared to have rheumatoid arthritis, and the danger of worsening the condition by treating it with Compound F locally.

Dr. J. W. Beattie and Dr. A. Woodmansey described an investigation of the response of the skin temperature in rheumatoid arthritis to reflex vasodilatation before and after treatment with steroids. Changes in the electrical resistance of the skin and in the relation of superficial pain threshold to skin temperature had also been studied. It was hoped that electrical resistance might prove to have a characteristic pattern in rheumatoid arthritis.

Mr. R. Broomhead gave a very interesting demonstration by means of *x* rays of his results in the treatment of osteo-arthritis of the hip by two types of arthroplasty; the vitallium mould and the acrylic prosthesis. He illustrated a variety of problems encountered in both types of arthroplasty. In his experience the vitallium mould was more satisfactory in its long-term results as the acrylic head suffered from structural defects and a tendency to fragment in the patient's body.

FUTURE ARRANGEMENTS

Heberden Oration, 1954.—Dr. Robert Stecher (*Cleveland, Ohio*) will deliver the Oration for 1954 on "Heberden's Nodes", on September 24 at the Post-Graduate Medical School of London, Hammersmith Hospital, Ducane Road, W.12, at 5 p.m. All members of the medical profession are cordially invited to be present.

A Clinical Meeting will be held on September 25 at the Post-Graduate Medical School at 10 a.m. Papers will be presented by the following:

Dr. Malcolm Thompson (*Edinburgh*): "Kerato-conjunctivitis Sicca and Rheumatoid Arthritis".

Dr. Rita Lackner and Dr. G. R. Fearnley (*London*), followed by Dr. A. K. Missen and Dr. Jean Turner (*London*): "Amyloidosis in Rheumatoid Arthritis".

Dr. G. O. Storey (*London*): "Paraplegic, Para-articular Calcification".

Dr. Rita Lackner, Miss J. Purkiss, and Dr. G. R. Fearnley (*London*): "Diphenylamine Reaction in Rheumatoid Arthritis".

Dr. G. R. Fearnley, Dr. E. G. L. Bywaters, Dr. Rita Lackner, and Dr. I. Meanock (*London*): "Comparison of Procaine and Hydrocortisone given by Intra-articular Injection in Rheumatoid Arthritis".

Dr. A. Aronoff (*London*): "Pulmonary Changes in Rheumatoid Arthritis".

The Annual General Meeting will be held on December 3 and 4, 1954, at the Royal College of Surgeons, Lincoln's Inn Fields, W.C.2. The main topic for discussion on the first day will be the results of the Empire Rheumatism Council's Cortisone/Aspirin trial. A symposium on Osteo-Arthritis will be held on the second day. Members wishing to present papers on this or other subjects should communicate with Dr. G. R. Fearnley, M.R.C.P., Post-Graduate Medical School of London, Ducane Road, W.12.

H.R.H. the Princess Royal has graciously consented to be present as the chief guest at the Annual Dinner on December 4, 1954.

* In this issue, p. 233.

CANADIAN RHEUMATISM ASSOCIATION

OFFICERS, 1954-55

Past-President: Louis G. Johnson (*Montreal, Quebec*)

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Wallace Graham (*Toronto, Ont.*)

UNIVERSITY OF HAVANA

SUMMER SCHOOL, 1954

A course in rheumatology embracing every aspect of research and treatment was held from July 20 to August 6, 1954, at the Nuestra Señora de las Mercedes University Hospital, under the direction of Dr. Victor Santamarina, with the assistance of Drs Fernando Salas Panisello (anatomy and pathology), José Alonso Suárez (radiology), Ernesto Roces García (rheumatology), and Horacio de la Torre (acute rheumatism and cardiology).

SOCIETÀ ITALIANA DI REUMATOLOGIA

SECOND ACQUI PRIZE, 1954

The international commission for the award of the second Acqui Prize of L. 1,000,000 met on June 19, 1954. The judges were Prof. L. Antognetti (*Genoa*), Prof. P. Barceló (President of the Ligue Européenne contre le Rhumatisme), Prof. P. Bastai (*Turin*), Prof. L. Justin-Besançon (*Paris*), Prof. F. Quaglia (*Acqui*), Prof. L. Villa (*Milan*), Prof. K. Walthard (*Geneva*), and Prof. A. Robechi (*Turin*). Prof. Barceló was elected chairman of the commission.

All the entries were of real merit and importance, and it was found very difficult to decide upon the best. After a long discussion it was decided to divide the prize equally between two contributions:

Prof. S. de Sèze (*Paris*): The Lumbo-Sacral Articulation.

Dr. F. Delbarre and Dr. F. Cayla (*Paris*): Biological Tests in Rheumatism.

The entry sent in by Drs D. Scopinaro, R. Rivano, and S. Solari (*Genoa*) was also judged worthy of special mention, and is to be published in the French, German, Italian, and Spanish journals of rheumatology.

ARTHRITIS AND RHEUMATISM FOUNDATION, U.S.A.

The Cleveland Chapter of the Arthritis and Rheumatism Foundation and the regional members of the American Rheumatism Association are sponsoring a conference devoted to rheumatic disease, to be held at the Hotel Carter, Cleveland, Ohio, on November 10, 1954, to which all physicians are invited (registration fee, ten dollars). The conference will be followed by a banquet to which lay members of the Arthritis and Rheumatism Foundation are invited. The speakers and their topics will be as follows:

T. Duckett Jones (*New York City*): Diagnosis of Rheumatic Fever.

C. H. Rammelkamp (*Cleveland, Ohio*): Prevention and Treatment of Rheumatic Fever.

A. B. Gutman (*New York City*): Diagnosis and Treatment of Gout.

C. L. Short (*Boston, Mass.*): Diagnosis of Rheumatoid Arthritis.

W. D. Robinson (*Ann Arbor, Mich.*): Treatment of Rheumatoid Arthritis.

W. Solomon (*Cleveland, Ohio*): Nature and Treatment of Osteo-Arthritis.

H. Worley Kendell (Peoria, Ill.): Rehabilitation of the Arthritic.

Inquiries should be addressed to William S. Clark, M.D., Chairman, 2073 Abington Road, Cleveland, 6, Ohio.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Non-Articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with steroid research which, although not directly concerned with the rheumatic diseases, may make an important contribution to knowledge of the scope and *modus operandi* of steroid therapy.

Acute Rheumatism

Clinical and Experimental Studies of the Mode of Action of Heparin in Rheumatic Fever. (Ricerche clinico-sperimentali sul meccanismo d'azione dell'eparina nella malattia reumatica.) MATTEIS, F. DE, and PANIGATTI, F. (1954). *Minerva med.* (*Torino*), **45**, 58. 1 fig., 33 refs.

The inhibitory action of salicylates on hyaluronidase has been attributed to liberation of heparin in the tissues, and favourable results have been reported from the administration of heparin and similar anticoagulants in the treatment of rheumatism. These have been explained as being due to either an anti-exudative effect through osmotic and diffusional regulation, or to an anticoagulant effect diminishing antigen-antibody reactions, an anti-hyaluronidase action, or an anti-anaphylactic action. In this study, carried out at the Institute of Clinical Paediatrics, University of Genoa, three lines of enquiry were pursued:

(1) the relative tolerance to heparin of rheumatic and non-rheumatic children;

(2) the effect of hyaluronidase on clotting factors *in vitro*;

(3) the relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances.

Heparin tolerance of non-rheumatic control patients and a group of fifteen salicylate-treated rheumatic children was estimated by comparing the coagulation times at 10, 30, and 60 min. after intravenous injection of 2,000 units of heparin. The non-rheumatic patients showed an average coagulation time of 37 seconds at 10 min., compared with 30 seconds in the rheumatic group. Since five non-rheumatic and two rheumatic patients had coagulation times of 50 seconds or over at 10 min., this estimation was used as a screening test for heparin treatment.

The effect of hyaluronidase on clotting factors *in vitro* was then investigated. Samples of blood from ten children free from haematological disease were examined for prothrombin time (in the presence of progressive dilutions of thrombokinase), for recalcification time, and for antithrombin time, and the effect on these figures of distilled water and hyaluronidase in solutions of 25 and 1·25 units per ml. determined. Prothrombin and recalcification times were prolonged and the antithrombin time little affected. (As these results were similar to those obtained with heparin, the effects of a heparin-hyaluronidase mixture were not investigated.)

Lastly, the relation between hyaluronidase, heparin, and salicylate in regard to intradermal diffusion of coloured substances was investigated, mixtures of fluorescein and distilled water and fluorescein and hyaluronidase being viewed by ultraviolet light through Wood's glass in two groups of subjects—non-rheumatic children injected with heparin and rheumatic children under salicylate treatment. The figures for increase in areas of spread with hyaluronidase in non-rheumatic cases were 226 to 285 sq. mm., and with distilled water 178 to 224 sq. mm.; in the cases of rheumatism being treated with salicylates the figures were 215 to 264 sq. mm. with hyaluronidase, and 195 to 237 sq. mm. with distilled water. The authors suggest that these differences indicate that salicylate has a greater anti-hyaluronidase effect than heparin. [The differences, however, are not statistically significant.] *W. A. Bourne.*

Determination of C-reactive Protein in Serum as a Guide to the Treatment and Management of Rheumatic Fever. STOLLERMAN, G. H., GLICK, S., PATEL, D. J., HIRSCHFELD, I., and RUSOFF, J. H. (1953). *Amer. J. Med.*, **15**, 645. 6 figs, 12 refs.

Tests for the presence of C-reactive protein (C.R.P.) in the serum of 62 patients with rheumatic fever were carried out at Irvington House and New York University College of Medicine, the patients being grouped according to the stage of rheumatic activity as follows:

(1) active rheumatic fever, 35;
(2) low-grade rheumatic activity, 11;
(3) "doubtful activity", 11;
(4) "pure chorea", 5.

Observations were continued during treatment with

various antirheumatic agents (including ACTH and cortisone) and during 6 months' convalescence. C.R.P. was present in the blood of nearly all the clinically active cases, and in six of the eleven doubtful cases, but was absent from all five cases of "pure chorea". Disappearance of C.R.P. from the blood is believed to indicate the termination of a rheumatic attack, while persistence of C.R.P. during treatment indicates inadequate suppression of the inflammatory process.

It is concluded that the presence of C.R.P. in the blood of a rheumatic patient is an extremely sensitive and reliable indication of rheumatic activity, but it is emphasized that its appearance is a non-specific response to many inflammatory processes. In certain isolated rheumatic conditions—for example, chorea, erythema marginatum, and subcutaneous nodules—there may be no C.R.P. in the patient's blood. *Kathleen M. Lawther.*

Ballistocardiogram in Acute Rheumatic Fever. ABRAMS, W. B., and CHESLEY, G. L. (1954). *Circulation (N.Y.)*, **9**, 400. 2 figs, 20 refs.

Ballistocardiograms were recorded at a U.S. Army hospital from eighteen young adult males suffering from acute rheumatic fever, thirteen of whom had clinical evidence of carditis. Of the 33 ballistocardiograms recorded from these thirteen patients, 31 were normal, one showed slight abnormalities, and one was considered dubious because of low voltage. Of twelve ballistocardiograms from five subjects without overt cardiac involvement, eleven were normal and one showed slight abnormalities. Records obtained when the activity of the disease was subsiding were normal in all but two cases. Case histories and ballistocardiographic tracings are presented.

The authors conclude that the ballistocardiogram is normal in most mild cases of rheumatic fever, even when there is clinical and electrocardiographic evidence of active carditis. *J. F. Goodwin.*

***para*-Acetylaminosalicylic Acid in the Treatment of Rheumatic Fever.** (L'acido para-acetilaminosalicilico nel trattamento della malattia reumatica.) BERTOLANI, F. (1954). *Minerva med. (Torino)*, **1**, 567. 11 figs, 25 refs.

As part of a study undertaken at the University of Modena of the relation between the delaying effect of certain drugs on erythrocyte sedimentation *in vitro* and their anti-rheumatic action, the anti-rheumatic effects of the N-acetyl derivative of *para*-aminosalicylic acid (APAS) have been studied. The authors have also carried out experiments, chiefly pharmacological, on this substance, on the diacetyl derivative (DAPAS) and on the acid itself (PAS). APAS has the greatest effect on erythrocyte sedimentation, DAPAS has a mild effect, and PAS has none.

APAS was used in the treatment of eight cases of rheumatic polyarthritis in the acute phase, seven of the patients being in hospital and one an out-patient, the dose varying from 10 to 25 g. daily. In four cases salicylates had been given previously without effect. In all cases the effect of APAS was to reduce the temperature, and relieve the pain, while the signs of cardiac and respiratory distress abated. Signs and symptoms tended to recur if the drug was stopped too soon. When DAPAS was given the effects were the same, as was to be expected since, according to the authors, both DAPAS and PAS are transformed into APAS after ingestion to an extent which depends on a variety of circumstances.

Experimentally, both the sodium salt of APAS and sodium salicylate reduced artificially produced fever in rabbits, PAS being less reliable, but none of the PAS derivatives appeared to have any analgesic properties when tested on rats with infra-red radiation as the painful stimulus. It was shown that APAS (but not PAS) delayed the urinary excretion of phenyl-sulphonephthalein, which had previously been injected into the talocrural joint of a rabbit; this property is found also in sodium salicylate and other anti-rheumatic substances.

The author considers that the conflict of opinion on the value of PAS in rheumatism may stem from the fact that its therapeutic effect depends on the degree of its conversion into APAS, which may vary from 30 to 85 per cent. *J. G. Jamieson.*

Dietary Eggs and Rheumatic Fever. WALLIS, A. D. (1954). *Amer. J. med. Sci.*, **227**, 167. 10 refs.

Evidence is accumulating which supports the theory that rheumatic fever is caused by a tissue sensitivity reaction to some product of the Group-A β-haemolytic streptococcus. One of the two haemolysins produced by this organism, streptolysin S, is inhibited by a substance present in the serum of all individuals, sick or well, the inhibition being of a physico-chemical nature rather than the result of an antigen-antibody. The strength of this inhibiting substance varies from individual to individual, and is dependent in part on the concentration of the serum of phospholipid, one of the ingredients of which is choline. Since the body can neither synthesize nor store choline in any significant quantity, the serum phospholipid level must depend on the dietary intake of choline, by far the richest source of which is egg. The author therefore estimated the egg intake in childhood of 184 subjects with rheumatic heart disease and compared it with that of 1,380 unaffected persons interviewed at the Pennsylvania Hospital, Philadelphia. Of the affected subjects, 10·2 per cent. actively disliked eggs and 40·6 per cent. believed that their consumption of eggs in childhood had been relatively small, the corresponding figures being 4·6 per cent. and 16·3 per cent. respectively in the control group. It is suggested that this difference in probable choline intake might have a bearing on the difference in susceptibility to rheumatic fever between the two groups. *R. S. Illingworth.*

Serum Phospholipid and Rheumatic Fever. WALLIS, A. D., and VIERGIVER, E. (1954). *Amer. J. med. Sci.*, **227**, 171. 2 figs, 26 refs.

In a further study of the relation between the phospholipids in the serum and susceptibility to rheumatic fever the authors determined the serum phospholipid level in 178 patients with inactive rheumatic heart disease. It was found that the level was below the average for normal individuals of the same age group in approximately two-thirds of these cases. Of 51 patients who had had more

than one attack of rheumatic fever, 46 had either an abnormally low serum phospholipid level or a history of an unusually low intake of eggs in childhood.

It is suggested that rheumatic fever may be produced "when a hemolytic streptococcal infection engenders more streptolysin S than the natural serum inhibitor, as a reflection of serum phospholipid, is able to neutralize".

R. S. Illingworth.

A Follow-up Study of Suspected Rheumatic Fever Patients. McCUE, C. M. (1954). *J. Pediat.*, **44**, 290. 8 refs.

In the past 11 years 2,678 new patients have been seen in the Medical College of Virginia Rheumatic Fever Clinic. In this group, 236 were listed as "deferred" after a complete initial study. Follow-up data have been obtained on 209 of these 236 cases.

The complaints and suspicious signs which were the reason for deferral are listed and compared with those [occurring in the 29 patients] later developing clear rheumatic fever. [This comparison shows a significantly higher incidence in the latter group of painful joints with swelling, fever, epistaxis, suspicious choreiform movements, increased erythrocyte sedimentation rate, electrocardiographic abnormality, and tachycardia.]

After an average follow-up period of 28 months, the following diagnoses have emerged:

Rheumatic fever .. .. .. (2·4 per cent. with rheumatic heart disease)	13·88 per cent
Rechecked and no rheumatic fever or heart disease found ..	66·98 per cent.
Local medical doctor says no rheumatic fever	9·09 per cent.
Nurse says patient well	3·83 per cent.
Diagnosis still deferred after recheck	6·22 per cent.

The excellent prognosis in this group as a whole makes strict diagnostic criteria imperative.—(*From the author's summary.*)

Hormone Therapy in 22 Cases of Rheumatic Fever. (Une expérience d'hormonothérapie dans la maladie de Bouillaud (22 cas).] GAUFROY, B. (1954). *Rev. Rhum.*, **21**, 35. 1 fig.

Prevention of Acute Rheumatism in Children. (La prévention de la maladie de Bouillaud chez l'enfant.) ROUVEIX, J. (1954). *Presse méd.*, **62**, 399.

Pathogenesis of Rheumatic Fever. LONG, D. A. (1954). *Lancet*, **1**, 529. 4 figs, bibl.

Chronic Articular Rheumatism

(Rheumatoid Arthritis)

Epidemiological Study of Rheumatoid Arthritis associated with Characteristic Chest X-Ray Appearances in Coal-Workers. MIALL, W. E., CAPLAN, A., COCHRANE, A. L., KILPATRICK, G. S., and OLDHAM, P. D. (1953). *Brit. med. J.*, **2**, 1231. 5 figs, 22 refs.

In this epidemiological study, carried out by members of the Medical Research Council Pneumoconiosis Research Unit, of a syndrome recently described by Caplan (*Thorax*, 1953, **8**, 29) in which rheumatoid arthritis is associated with nodular fibrosis of the lung, chest radiographs of miners in the Rhondda Fach, South Wales, were re-examined. From among those showing massive fibrosis or tuberculosis, all films (20) which were thought also to show "rheumatoid"-type opacities were selected, sixty other films not showing these characteristics being used as controls. The twenty miners from whom the characteristic films were obtained were visited, questioned, and their joints examined if the history suggested arthritis; the criteria for the clinical diagnosis of arthritis are given. In addition, all men considered (in a previous survey) to have rheumatoid arthritis, as well as the twenty selected as having "rheumatoid" radiological appearances in the chest, were fully investigated.

It was found that the incidence of rheumatoid arthritis was higher (3 per cent.) among miners having massive fibrosis or tuberculosis than among the general population (0·42 per cent.), while its prevalence in the group showing "rheumatoid" opacities in the chest film was 55 per cent. (No clinical evidence of rheumatoid arthritis was found in the whole series save in these two groups.)

The activity, severity, and duration of the arthritis was not correlated with the degree of typical "rheumatoid" radiological appearance. It was also noted that the rheumatoid lung lesions may either precede the onset of arthritis or develop subsequently. Total dust exposure may be a significant factor in determining the occurrence of rheumatoid arthritis, and it was noted that a high prevalence of arthritis occurred in men exposed to stone dust. Clinical examination of the group showed evidence of pulmonary tuberculosis in only one man.

One case in which the chest radiograph showed rheumatoid lesions came to necropsy during the investigation; the findings are detailed. The pulmonary lesions consisted of whorled, yellowish-white, collagenous fibrous tissue, with central softening but no evidence of tuberculosis, and resembled those described by Gough under the name of "infective nodules". Although the findings at this necropsy did not confirm the presence of tuberculous infection, five other necropsies of men with rheumatoid arthritis (in whom the *x*-ray appearances were less typical) have yielded evidence of it. Also, from two men with "rheumatoid" chest lesions and proved tuberculosis, atypical bacilli were isolated, which produced tuberculosis on injection into guinea-pigs. The condition may therefore be one in which the tubercle bacilli are modified.

It is suggested that the hypotheses that:

(*a*) these appearances are coincidental and merely a manifestation of the rheumatoid syndrome,
(*b*) that the pathological changes play the part of a chronic septic focus,
are unlikely.

The authors conclude that there must be some other factor, and that the predisposition to form these lung lesions may be an expression of an unusual type of tissue reaction to dust and tuberculosis in miners who are predisposed to rheumatoid arthritis.

[The methods and criteria of examination and of evaluating observer-error are discussed in an appendix to the paper.] *L. W. Hale.*

Long-Term Treatment of Rheumatoid Arthritis with *para*-Aminobenzoic Acid and Cortisone Acetate. WIESEL, L. L., and BARRITT, A. S. (1954). *Amer. J. med. Sci.*, **227**, 74. 15 refs.

In previous communications (*Brooklyn Hosp. J.*, 1950, **8**, 148, and *Amer. J. med. Sci.*, 1951, **222**, 243; *Abstracts of World Medicine*, 1951, **9**, 643, and 1952, **11**, 81) these authors have reported the synergistic action of *para*-aminobenzoic acid, given by mouth, and cortisone acetate, given by intramuscular injection. In this paper from the Brooklyn Hospital, New York, they report the effects of the combined oral administration, over a period of one year or more, of cortisone acetate and the sodium or potassium salt of *para*-aminobenzoic acid to 31 patients with rheumatoid arthritis. Their impression is that combination with *para*-aminobenzoate increases the anti-inflammatory action of a given dose of cortisone acetate two- to three-fold, and that such increased potentiation is not accompanied by a similar increase in the incidence of side-reactions or complications.

W. S. C. Copeman.

Comparison of Cortisone and Codeine Medication as an Adjuvant to Manipulation in Rheumatoid Arthritis. SUBCOMMITTEE OF THE MEDICAL RESEARCH COUNCIL/NUFFIELD FOUNDATION JOINT COMMITTEE ON CORTISONE AND ACTH IN CHRONIC RHEUMATIC DISEASES. (1954). *Brit. med. J.*, **1**, 233. 1 fig.

The purpose of the investigation here reported was to compare the effect of cortisone with that of compound codeine tablets (*B.P.*) in relieving the pain and curtailing the period of increased disability following the manipulation under a general anaesthetic of the flexed knees of patients suffering from rheumatoid arthritis. Four different centres took part, and 33 patients with flexion deformities of the knees of at least 6 months' duration were admitted to the trial, eighteen receiving cortisone and fifteen the tablets. To both groups the drug was given on the day before manipulation, on the day of manipulation, and for 14 subsequent days. The dose of cortisone was 200 mg. on the first day, 300 mg. on the day of manipulation, and on the third day, 200 mg. on the fourth and fifth days, 150 mg. for the next 3 days, 100 mg. for the next 2 days, and 50 mg. for the last 6 days. Two compound codeine tablets were given 3 times a day to the other patients.

After manipulation the knee was put in plaster, which was bivalved after 24 hours, the posterior shell only being retained. Assessments of the patient's condition were made on the 5 days before and 5 days after manipulation, and then at 5-day intervals until the 26th day after admission to the trial. The assessments were all made by the same group of observers, and covered pain on pressure, pain on active and passive movement, range of movement, circumference of the knee, skin temperature, and the time taken to carry out complete flexion and extension five times with the heel supported on a skate in the horizontal position. From the results of the trial, which are given in the form of tables and a chart, it was concluded that "cortisone revealed no advantage over tab. codeine co. as a cover for manipulation of the knee".

[This report has evoked much discussion; it is important to note that the investigation was made only into the effect of these preparations on the sequelae of manipulation of a flexed knee, not into their effect on the disease as a whole.] *W. Tegner.*

Use of Phenylbutazone in Rheumatoid Arthritis. PEMBERTON, M. (1954). *Brit. med. J.*, **1**, 490. 12 refs.

Phenylbutazone was tried at Withington Hospital, Manchester, in the treatment of 186 patients with chronic polyarthritis of the rheumatoid type and 24 with degenerative hip disease. During the investigation, which did not include a control series of cases, other forms of treatment, including gold injections, were continued. In assessing the results the effect of rest in bed was discounted. The average dose of phenylbutazone was 600 mg. daily. Patients were examined before, and 3 and 6 months after, beginning treatment. Subjective improvement was judged by the patient's capacity for, and comfort during, normal activity.

After 3 months' treatment, the condition of 156 patients was reviewed. It was found that the drug was of "little or no value" in 36, of "moderate value" in 104, and of "considerable benefit" in sixteen. The erythrocyte sedimentation rate was apparently not affected. Toxic reactions occurred in 92 cases, about 25 per cent. of all patients having to cease treatment on this account. Reactions consisted in gastro-intestinal symptoms, including gastric haemorrhage, rash, oedema, fever, soreness of the mouth, and a few, infrequent manifestations of doubtful origin. There was no correlation between the serum level of phenylbutazone and the incidence of toxic reactions. *G. Loewi.*

Results of Treatment of Rheumatoid Arthritis with Polyvalent Autovaccines. (Résultats du traitement de la polyarthrite chronique évolutive par l'autovaccinothérapie totale.) PRÉVOT, A.-R. (1954). *Bull. Acad. Méd. (Paris)*, **138**, 120. 2 refs.

Oral Hydrocortisone in the Treatment of Rheumatoid Arthritis. BOLAND, E. W. (1954). *Med. Clin. N. Amer.*, **38**, 337. 26 refs.

Clinical Study of Chrysotherapy in Rheumatoid Arthritis. (Contributo clinico alla crisoterapia dell'artrite reumatoide.) FARNETI, P., and MICCOLI, G. (1954). *Reumatismo*, **6**, 148. 1 fig., 37 refs.

Use of Trypsin in Rheumatoid Arthritis: A Clinical Study. GOODSON, W. H., ROSE, D. L., and ALYEA, W. S. (1954). *J. Kans. med. Soc.*, **55**, 129. 2 refs.

Haematological Effects of Rheumatoid Arthritis. (Sull' impronta ematologica dell'-artrite reumatoide.) LENTINI, D., and ROSSI, G. (1954). *Reumatismo*, **6**, 167. 24 refs.

Musculo-Skeletal Function in Rheumatoid Arthritis. PRESTON, R. L. (1954). *Maryland med. J.*, **3**, 112. 10 figs, 3 refs.

Neurovegetative Investigations in Rheumatoid Arthritis. (Saggi neurovegetativi nell'-artrite reumatoide.) ROSSI, G. (1954). *Reumatismo*, **6**, 182. 15 refs.

Early Radiological Signs of Rheumatoid Arthritis. (À propos des signes radiologiques précoces des polyarthrites.) ISEMEIN, L., and FOURNIER, A. (1954). *Rhumatologie*, **No. 1**, 16.

(Osteo-Arthritis)

Initial Stages of Osteo-Arthritis. (Les étapes initiales de la maladie arthrosique.) JUSTIN-BESANÇON, L., RUBENS-DUVAL, H., and VILLIAUMEY, J. (1954). *Rhumatologie*, **No. 1**, 1.

Recognition and Management of Degenerative Joint Disease. FERCIOT, C. F. (1954). *Geriatrics*, **9**, 121.

Osteo-Arthritis of the Hip. Diagnosis and Treatment. (La coxarthrose, diagnostic et traitement.) BRAILSFORD, J. F. (1954). *Rhumatologie*, **No. 1**, 10. 3 refs.

Effusion into the Joint in Osteo-Arthritis of the Knee. (Épanchement artículaire et gonarthrose.) ARLET, J., and MOREAU, G. (1954). *Rev. Rhum.*, **21**, 132. 3 figs, 8 refs.

(Spondylitis)

Unrecognized Late Forms of Bechterew's Disease [Ankylosing Spondylitis]. (Unerkannte Spätformen der Bechterewschen Erkrankung.) MARTICKE, G. (1954). *Dtsch. med. Wschr.*, **79**, 507. 3 refs.

This study was carried out at the Balneological Institute at Bad Nenndorf where, it is claimed, some 200 cases of ankylosing spondylitis are treated every year. Of 195 cases referred for treatment in 1952, twelve had been either misdiagnosed or only belatedly recognized. On going into the reasons for this delay in diagnosis it was found that twelve patients could be divided into four groups, case histories representative of each being given. In the first group pain was not a prominent feature and attention had finally been drawn to the spine by increasing deformity; in the second group a polyarthritis had overshadowed the spinal signs and symptoms; in the third group an industrial accident had been held responsible for symptoms which would otherwise have been investigated more closely; and in the last group the symptoms distributed over various parts of the spinal column, were so mild that they had been ascribed to "muscular rheumatism".

Treatment in such long-standing cases should be both general and local, gold injections and *x*-ray therapy being suggested; breathing and remedial exercises are also advisable. Balneotherapy is regarded as an ideal combination of general and local treatment, but must be continued for many years until the disease process is finally arrested. *D. Preiskel.*

Ankylosing Spondylitis and Pulmonary Tuberculosis. (Spondilite anchilosante e tubercolosi polmonare.) BARBASO, E., and EINAUDI, G. (1954). *Reumatismo*, **6**, 176. 19 refs.

(Miscellaneous)

Effect of Splenectomy in Acute Systemic Lupus Erythematosus. JOHNSON, H. M. (1953). *Arch. Derm. Syph. (Chicago)*, **68**, 699. 3 figs, 27 refs.

The author reports the results of splenectomy in twelve cases of acute systemic lupus erythematosus seen in Hawaii, where the disease is common among the Japanese and Chinese inhabitants. He points out that hypersplenism is the probable cause of the thrombocytopenia, granulocytopenia, and anaemia which are sometimes severe in this disease, and that these haematological manifestations constitute the main indications for splenectomy.

In two cases the operation was performed as an emergency for acute thrombocytopenic purpura; after operation there was complete cessation of the haemorrhagic tendency, with dramatic clinical improvement. Anaemia and leucopenia were present in the remaining ten patients, two of whom also had thrombocytopenia, and splenectomy was performed during the active phases of the disease "as a desperate measure". Three of these patients died within 10 days of operation; in the remaining seven there was a varying degree of symptomatic relief, which, however, was maintained in only two. All but four of the twelve patients died from lupus erythematosus within one year of operation; one died 2½ years after operation, but three were alive 7, 3, and 2 years later respectively.

The operation was followed by an increase in the erythrocyte, leucocyte, and platelet counts. Histological examination of the spleen, which was enlarged in eight cases, showed concentric periarteriolar collagen lamination, sinus hyperplasia, and widened marginal zones of medium and large lymphocytes at the periphery of the Malpighian follicles.

[The majority of these cases were seen before the introduction of the L.E.-cell and L.E.-plasma tests, and the diagnosis was based upon the association of fever, polyarthritis, rashes, leucopenia, anaemia, thrombocytopenia, and albuminuria.] *Nigel Compston.*

Treatment of Lupus Erythematosus with Chloroquine Sulphate. HARVEY, G., and COCHRANE, T. (1954). *J. invest. Derm.*, **22**, 89. 1 fig., 1 ref.

Thirty cases of lupus erythematosus were treated with chloroquine sulphate ("nivaquine"). The results obtained are as good as those from mepacrine hydrochloride ("atabrine"). The drug is much less toxic and so far has caused no dermal complications. The mode of action of chloroquine sulphate is unknown but future lines of investigation are suggested.—[*Authors' summary.*]

Developmental Dysarthria. MORLEY, M., COURT, D., and MILLER, H. (1954). *Brit. med. J.*, **1**, 8. 2 refs.

The authors reserve the term "developmental dysarthria" for dysarthria which is not associated with neuromuscular disorders elsewhere, as in spastic diplegia. Boys are affected twice as often as girls, and in ten out of eighteen cases examined at the Royal Victoria Infirmary, Newcastle upon Tyne, there was a family history of a speech defect. Birth injuries, prematurity, and emotional disturbances do not appear to be responsible. In two-thirds of the authors' cases voluntary movements of the tongue, lips, or palate were manifestly spastic, but in the remaining one-third the abnormality of movement occurred only during speech, and these cases the authors regard as examples of "articulatory dyspraxia". Although the intelligence of the eighteen children studied was within the range of normal, in half of them there had been some delay in the development of language. The speech in cases of developmental dysarthria is slow, clumsy, and often explosive, and the response to treatment is usually slow. This is in marked contrast with cases of dyslalia, a term reserved by the authors for instances of temporary consonant substitution, in which language develops at the normal time, speech is fluent if unintelligible, and the response to treatment is rapid.

J. Foley.

Phenylbutazone Therapy. Relation between Toxic and Therapeutic Effects and the Blood Level. BRUCK, E., FEARNLEY, M. E., MEANOCK, I., and PATLEY, H. (1954). *Lancet*, **1**, 225. 2 figs, 12 refs.

The relation between the blood level of phenylbutazone given by mouth and the toxic and therapeutic effects was investigated at the West London Hospital, Hammersmith, in 52 patients, 48 of whom had rheumatoid arthritis and four had osteo-arthritis.

The blood level of phenylbutazone varied considerably in different patients on the same daily dosage. The average level, however, rose steadily when the dosage was increased, up to a maximum of 600 mg. daily; when it was increased beyond this to 1,200 mg. the blood level rose less quickly. Toxic effects were noted in 25 patients, but were mild in fifteen and did not call for cessation of treatment. There was a marked and statistically significant correlation between the incidence of side-effects and the blood level of the drug; when the blood level of phenylbutazone was more than 10 mg. per 100 ml. the incidence of side-effects was high (85 per cent.). One patient died from renal failure, possibly precipitated by the salt-retaining effect of phenylbutazone.

No objective improvement was observed in any of the patients, and the authors therefore had to rely on the subjective response to assess the therapeutic effect of the drug. On this basis, they found that when the blood level was below 5 mg. per 100 ml., two out of eight patients obtained relief of symptoms; when the level was between 5 mg. and 10 mg. per 100 ml., 25 out of 29 patients experienced relief of symptoms. At blood levels above 10 mg. per 100 ml. the therapeutic effect was not notably enhanced.

In another investigation the authors found that the blood level of phenylbutazone rose slowly, reaching a maximum in about 10 days. The drug was retained in the body, and when administration ceased, excretion continued for 10 to 21 days. Toxic effects may therefore persist or may even appear after the drug has been discontinued.

The authors consider that phenylbutazone is most effective at a blood level of 5 to 10 mg. per 100 ml., but because of individual variations in absorption a fixed scheme of dosage cannot be laid down. They suggest that a dose of 200 mg. daily should be given initially, increased by 100 mg. daily until the response is satisfactory. With doses of more than 400 mg. daily the likelihood of serious toxic reactions increases rapidly.

B. E. W. Mace.

Injectable Phenylbutazone in Rheumatism. (La phénylbutazone injectable en rhumatologie.) DE SÈZE, S., and LEVERNIEUX, J. (1954). *Presse méd.*, **62**, 203.

The authors report their results in 700 cases of rheumatism which, since January, 1952, they have treated with phenylbutazone given parenterally. The conditions for which the drug was administered included gout, rheumatoid arthritis and spondylo-arthritis, tendinitis and tendino-bursitis, arthroses, and radiculalgia. The general plan of treatment was to begin with a course of intravenous infusions of 1 g. phenylbutazone in a 10 per cent. solution given daily, or on alternate days. As symptoms subsided, usually in the second week of treatment, intramuscular injections of a similar dose of phenylbutazone, with triethylene glycol and procaine, were substituted for the infusions, and these were also given daily or on alternate days. Subsequently, the intervals between injections were gradually increased, until for chronic cases individual maintenance doses were established.

The best results were observed in cases of gout and ankylosing spondylitis. In cases of rheumatoid arthritis they were inconstant. With adequate dosage, the maximum effect of the drug was observed from the beginning of treatment. The authors regard the following three precautions as indispensable:

(1) the patients should be carefully selected, cachectic cases and those having an abnormal blood picture or a history of gastric and cardio-renal disease being excluded;

(2) during treatment a strict sodium-free diet must be enforced;

(3) treatment should be suspended at the first sign of complications, such as digestive disturbances, peripheral oedema, haemorrhage, or cutaneous eruptions.

A. Swan.

Stigmonene Bromide in the Treatment of Muscular Spasm. MULHOLLAND, H. F., and O'CONNELL, J. H. (1954). *J.-Lancet*, **74**, 90. 2 figs, 20 refs.

"Stigmonene" bromide is a synthetic alkaloid-like salt of the quaternary pyridinium series having a slightly less powerful cholinergic action than neostigmine but the advantage of being of lower toxicity. This drug was given parenterally in doses of 0·5 to 4 mg. twice weekly to 64 out-patients attending St. Vincent's Hospital, New York, for the treatment of muscular spasm associated

with osteo-arthritis, rheumatoid arthritis, and allied conditions.

Increased range of joint movement and decrease of pain was obtained in thirty (53 per cent.) of 55 patients followed up, and this improvement was maintained in eleven (61 per cent.) of eighteen treated during the following 10 weeks with saline injections as a placebo. Side-effects, which were minimal and were relieved by oral administration of atropine, included abdominal distress, paraesthesiae, muscular weakness, aggravation of the arthritis (two cases), and syncope (one case, doubtfully attributable to the stigmonene). It is emphasized that these cases were far advanced and unlikely to respond dramatically to any form of therapy. The optimum dose of the drug was considered to be 3 or 4 mg. twice weekly.

I. Ansell.

Phenylbutazone in the Management of Rheumatoid Arthritis, Rheumatoid Spondylitis, and Gouty Arthritis. MacKnight, J. C., Irby, R., and Toone, E. C. (1954). *Geriatrics*, **9**, 111. 16 refs.

Treatment of Rheumatism with Minimal Doses of Hormones administered subcutaneously by means of Hyaluronidase. Technique and Results. (Hormonoterapia antirreumatica con dosis minimas administradadas por perfusion subcutanea, por medio de la hialuronidasa. Tecnica y sus resultados.) Weil, M.-P., Sichère, R. M., and Gassot, B. (1954). *Folia clin. int.* (*Barcelona*), **4**, 74.

Articular Rheumatism, Steroid Hormones, and Salicylic Acid. (Gelenkrheumatismus, Steroidhormone und Salizylsäure.) Bauer, J. (1954). *Münch. med. Wschr.*, **96**, 309. 4 figs.

Intra-Articular Hydrocortisone in the Management of Rheumatic Diseases. Hollander, J. L., Brown, E. M., and Jessar, R. A. (1954). *Med. clin. N. Amer.*, **38**, 349. 1 ref.

Clinical and Aetiological Study of Talalgia. (Étude clinique et étiologique sur les talalgies.) Lièvre, J. A., and Cohen, M. (1954). *Rev. Rhum.*, **21**, 109. 6 refs.

Interspinous Pseud-arthrosis (Baastrup's Disease) (Neartrosis interespinosa (enfermedad de Baastrup).) Vilaseca, J. M., Barceló, P., and Casademont, M. (1953). *Rev. esp. Reum.*, **5**, 101. 13 figs, 15 refs.

Disk Syndrome

Myelopathies associated with Cervical Osteo-Arthritis. (Les myélopathies chroniques sous-jacentes aux cervicarthroses.) Bonduelle, M. (1954). *Rev. Rhum.*, **21**, 22. 8 figs, 16 refs.

Chemistry, Structure, and Function of the Intervertebral Disk as a Basis for the Understanding of its Pathological Changes. (Chimie, structure et fonction du disque intervertébral, bases de compréhension de ses modifications pathologiques.) Hartmann, F. (1954). *Rev. Rhum.*, **21**, 1. 15 figs, 26 refs.

Gout

Effect of Phenylbutazone on Uric Acid Metabolism. Mason, R. M. (1954). *Brit. med. J.*, **1**, 788. 5 figs, 10 refs.

It has been claimed that phenylbutazone causes a striking diminution in the serum uric acid level in acute gout. The author has studied the effect of the drug in five cases of acute gout at Chase Farm Hospital, Enfield, Middlesex. He states that a specific effect on uric acid metabolism and on acute gout would be unique.

In the first case administration of 600 mg. daily of phenylbutazone resulted in a fall in the blood uric acid level from 11·6 mg. to 4·3 mg. per 100 ml. by the tenth day; there was excess excretion of uric acid amounting to 1,485 mg. during the 10 days.

In the second case the serum uric acid level fell from 4·7 mg. to 3·5 mg. per 100 ml. in 7 days, the excess uric acid excreted being 620 mg.

In the third case the total excess of uric acid excreted was 2,254 mg. in 7 days, but the serum level fell only from 5·4 mg. to 4·8 mg. per 100 ml.

The plasma uric acid level did not fall in the fourth case, in which, moreover, an actual retention of 365 mg. uric acid was observed; there was appreciable water retention in this case.

The fifth patient had Paget's disease, but during the first week of phenylbutazone therapy the plasma uric acid level fell from 4·9 to 2·6 mg. per 100 ml. and the uric acid excreted amounted to 686 mg.

In the second, third, and fifth cases, the fall in the uric acid concentration in the serum was roughly equivalent to the amount excreted, assuming equal distribution in the body water, but in the first case the fall in the serum level was much greater than could be accounted for by the urinary excretion. It is suggested that the variable results were due to the water-retaining and uricosuric properties of the drug, and that a direct effect on uric acid metabolism has not been proved. *C. L. Cope.*

Clinical Study of 136 Cases of Gout in the Male. (Étude clinique de 136 cas de goutte masculine.) Serane, J., and Bonniot, R. (1954). *Presse méd.*, **62**, 507. 23 refs.

Butazolidin in the Treatment of Gout. With a Comparison with Other Agents. Steinbrocker, O., Neustadt, D. H., and Ehrlich, M. (1954). *Med. Clin. N. Amer.*, **38**, 611. 1 fig., bibl.

Non-Articular Rheumatism

Cortisone and Hydrocortisone (Compound F) in Treatment of the Painful Shoulder. Coventry, M. B. (1954). *Proc. Mayo Clin.*, **29**, 58. 7 refs.

Encouraged by the good results obtained with cortisone in the treatment of ten cases of periarthritis of the shoulder which had failed to respond to physiotherapy, the author extended this treatment to fifty similar cases, the results being reported in this paper from the Mayo Clinic. The drug was given by mouth in a dosage of 75 mg. a day for 3 to 4 weeks; in some cases, however, the

dose was reduced to 50 mg. or less after the first week. Improvement was usually noted after the first 24 to 48 hrs. Aspirin was given in addition if required. Manipulation was rarely necessary, but when it was performed cortisone was given after operation. The only side-effect was an exaggerated anxiety state in one patient. The author found that in general the more acute the periarthritis, the more satisfactory the result. In cases of calcific tendinitis, sprains, and degenerative changes in the long head of the biceps tendon and the musculo-tendinous cuff an injection of 25 to 50 mg. hydrocortisone was given, repeated if necessary in 3 to 5 days.

It is concluded that in diffuse conditions, such as periarthritis, cortisone supplemented with physiotherapy is the most satisfactory treatment. For more localized conditions injection of hydrocortisone is the treatment of choice, acute calcific tendinitis responding particularly well, and sprains and degenerative conditions rather less satisfactorily. *H. F. Turney.*

Pseudo-Polyarthritis of the Shoulder and Hip Girdles. (Pseudo-polyarthrite rhizomélique.) FORESTIER, J., and CERTONCINY, A. (1953). *Rev. Rhum.*, **20**, 854. 4 refs.

To the syndromes classed as "inflammatory rheumatism" the authors add one which they name *pseudo-polyarthrite rhizomélique*. This account of the condition is based on a study of 25 patients—seventeen women and eight men. Pain in both shoulders, abrupt in onset and preventing by its extreme severity all movement at the joints, associated with a lesser degree of pain and stiffness in the hips, a low-grade fever, and some loss of weight, are the most prominent clinical features of the syndrome, which affects individuals in the second half of life. It differs from the common scapulo-humeral periarthritis in being bilateral and symmetrical, and in its association with fever, loss of weight, raised erythrocyte sedimentation rate (E.S.R.), and pain and stiffness in the hips. It is not a form of rheumatoid arthritis, from which it differs strikingly in its localization exclusively to the roots of the limbs and in its evolution: there is no spread to other joints, the tendency being towards complete recovery with no residual signs. Also, by its clinical features and evolution it is readily distinguished from ankylosing spondylitis and from the shoulder-hand syndrome.

Treatment with copper and with gold has been tried. In cases of recent onset, intravenous "cupralene" was given intravenously in doses of 250 mg. twice weekly to a total of 2 to 3 g. Nearly all the patients so treated improved rapidly, the E.S.R. falling to normal within a few months. Others were treated, with equally good results, with "alochrysine" in doses of 100 mg. weekly to a total of 1 to 1·5 g. in each course, with an interval of 6 to 8 weeks between the courses. Improvement was marked during the first course; by its end, pain had disappeared, the E.S.R. was normal, and only some slight stiffness of the shoulder remained. In all cases, cure resulted after one or two courses.

[Information concerning the course of the untreated disease would be helpful.] *Kenneth Stone.*

Checkrein Shoulder. A Type of "Frozen" Shoulder. Diagnosis and Treatment by Manipulation and ACTH or Cortisone. QUIGLEY, T. B. (1954). *New Engl. J. Med.*, **250**, 188. 6 figs, 12 refs.

The results of treatment of "Frozen" shoulders by manipulation under anaesthetic (Pentothal), with ACTH or cortisone given concurrently, are described. Of 29 shoulders treated, in 26 patients, ten regained normal function, thirteen were improved, and six were unimproved; the results were not significantly different, in those cases with a definite inflammatory or traumatic origin, to those occurring spontaneously.

The authors noted that their good results tended to occur in patients who presented a definite clinical picture of disuse stiffness following an acute episode of pain, followed by partial recovery of movement, and by a single, definite release of resistance at manipulation. They postulate that the syndrome is due to adhesion of the capsule of the shoulder joint, in its antero-inferior region, and suggest the term "checkrein shoulder".

Pain after manipulation was satisfactorily controlled by 40 mg. ACTH gel twice daily, for three days, or by oral cortisone, 300 mg. daily for 3-4 days, and then tapered off. Intensive active movements, together with exercises against resistance, were begun immediately after manipulation, interspersed with periods of rest, with the hands clasped behind the head. It is stressed that manipulation should be a gentle procedure, and should not be undertaken lightly. *B. E. W. Mace.*

Fibrositis and Non-Articular Rheumatism. GRAHAM, W. (1954). *Physiotherapy*, **40**, 101.

New Concept of "Humero-Scapular Periarthritis". (Nouvelle conception de la "periarthritis humero-scapularis".) AHRINGSMANN, H. (1954). *Rhumatologie*, **No. 1**, 14.

General Pathology

Liver Biopsy in Rheumatoid Arthritis. MOVITT, E. R., and DAVIS, A. E. (1953). *Amer. J. med. Sci.*, **226**, 516. 13 refs.

It has been suggested by Archer (*Ann. intern. Med.*, 1951, **34**, 1173) that the impairment of hepatic function frequently reported to occur in rheumatoid arthritis may well be due to the therapeutic agents commonly employed, many of which are hepatotoxic. The present authors describe their findings in seventeen cases of rheumatoid arthritis in men, who were subjected to needle-biopsy of the liver and various tests of hepatic function. They found no significant evidence of hepatic damage, even when the disease was of many years' standing.

A. C. Lendrum.

Some Aspects of the Aetiology of Rheumatic Diseases. (К вопросу об этиологии ревматической болезни) KASSIRSKAYA, E. G. (1953). *Ter. Arkh.*, **25**, 30. 16 refs.

The negative results of blood culture in many cases of

subacute bacterial endocarditis and most cases of rheumatic carditis are due, in the author's opinion, to the fact that the media commonly used do not meet the biological requirements of slow-growing micro-organisms capable of splitting carbohydrates with the formation of acid, since this acid, if allowed to accumulate, soon reaches a lethal concentration.

However, if media which contain natural albumin, such as Löwenthal's broth, semi-liquid agar with plasma, or Tarozzi's medium, are used and the cultures incubated for periods up to 2 months, *Streptococcus viridans* can be isolated in a very much higher proportion of cases. Thus the author was able to isolate *Strep. viridans* in thirty out of 36 cases of subacute bacterial endocarditis (83·3 per cent.), in eleven out of eighteen cases of primary or recurrent rheumatic carditis (61·1 per cent.), and in seventeen out of 43 cases of other forms of rheumatism.

These findings make it possible to regard all these diseases as of common aetiology. The isolation of the infecting organism is of importance also in the treatment of rheumatic diseases, as by determining its sensitivity the rational dose of penicillin can be ascertained.

H. W. Swann.

Role of the Reticulo-endothelial System in the Eosinopenic Reaction to Glucocorticosteroids. (Die Rolle des retikulo-endothelialen Systems für die eosinopenische Reaktion unter Gluco-Corticosteroiden.) ESSELLIER, A. F., MARTI, H. R., and MORANDI, L. (1954). *Acta haemat.* (*Basel*), **11**, 21. 5 figs, 29 refs.

The effect of blocking the reticulo-endothelial system in the guinea-pig on the peripheral eosinopenia normally produced by the injection of ACTH (corticotrophin) was investigated in experiments carried out at the Medical Clinic of the University of Zurich. Blocking was achieved by the subcutaneous injection of a 1 per cent. aqueous solution of trypan blue, which is stored in the reticulo-endothelial system, 2 ml. being given on the first day and then 1 ml. every other day up to a total of 18 ml. Male guinea-pigs of 500 to 700 g. were used, some with a normal eosinophil count (up to 360 per c.mm.), some with a constant increase up to 6,600 per c.mm. ACTH (10 units) or cortisone (0·625 mg./100 g. body weight) was given 24 hrs after the last injection of trypan blue, and changes in the eosinophil count compared with those in a significant number of control animals which had not received trypan blue. The experiments were planned and evaluated statistically.

It was found that the eosinopenic effect of ACTH and of cortisone was diminished considerably by blockage of the reticulo-endothelial system, or even suppressed entirely. When the dose of cortisone was increased to 2·5 mg./100 g., however, a significant fall in the eosinophil count was achieved even in animals treated with trypan blue.

This effect, being obtained with cortisone as well as ACTH, must be independent of the adrenal cortex. It is thus concluded that the reticulo-endothelial system plays an important part in the mechanism of the eosinopenia caused by glucocorticosteroids. *V. C. Medvei.*

Relation between the Number of Eosinophils in Blood and Bone Marrow under Ordinary Conditions and under the Influence of ACTH. [In English.] UHRBRAND, H. (1954). *Acta haemat.* (*Basel*), **11**, 11. 2 figs, 25 refs.

The investigation here reported was undertaken at the Frederiksberg Hospital, Copenhagen, to determine whether the number of eosinophil granulocytes in the bone marrow changes when the eosinophil count in the blood decreases under the influence of ACTH (corticotrophin). At the same time a study was made of the relation between the eosinophils of the blood and bone marrow under normal conditions, about which there has been considerable difference of opinion. For the latter purpose specimens of blood and bone marrow from 31 patients were examined; eight of these were suffering from allergic disorders (six from asthma and two from drug eruptions), while the remainder had various diseases, none of which was likely to affect the eosinophil count. It was found that a low count in the blood (expressed as percentage of the total leucocyte count) corresponded to a low count in the marrow (expressed as percentage of all nucleated cells), and that when the count was increased in the blood, there was also a higher count in the marrow. In the five patients whose blood showed the highest eosinophil counts the percentage was lower in the marrow, whereas in the remainder the marrow count was consistently slightly higher. The effect of ACTH was then observed on thirteen of the same patients, including the six asthmatics, blood and bone-marrow specimens being examined 4 to 6 hours after a single dose of 20 to 40 mg. ACTH, in nine cases also after 3 days' treatment with 20 mg. three times daily, and in one case also before and after a dose of cortisone. The eosinophil values were expressed as in the previous series as a percentage of the total leucocyte or nucleated-cell count. It was found that 4 to 6 hrs after the dose of ACTH the eosinophil count in the blood was decreasing, while that in the marrow was rising. The initial rise did not persist, however, and after 3 days' treatment the eosinophil count in the marrow was in no case greater than it had been before the ACTH had been given.

V. C. Medvei.

Evaluation of the Effects of Cortisone on the Subcutaneous Nodules of Patients with Rheumatoid Arthritis. ZIVIN, S., STECK, I. E., MONTGOMERY, M. M., KAISER, G. D., and BENNETT, G. A. (1954). *J. Lab. clin. Med.*, **43**, 70. 9 figs, 17 refs.

In this well-controlled study carried out at the University of Illinois College of Medicine, Chicago, by means of clinical observation, measurement, and histological examination of biopsy specimens of the subcutaneous nodules of rheumatoid arthritis it was shown that these nodules are commonly softened and reduced in size by the administration of cortisone, but that even over long periods of administration of the hormone there appeared to be no consistent modification of the histological picture. *A. C. Lendrum.*

Sensitized Sheep-Cell Agglutination Reaction in Rheumatoid Arthritis. ALEXANDER, R., and FOREST, G. K. DE (1954). *Amer. J. Med.*, **16**, 191. 3 figs, 14 refs.

Liver Function and Rheumatoid Arthritis. (Funzionalita epatica e malattie reumatiche.) ANDREINI, A. (1954). *Minerva med.* (*Torino*), **45**, 532. 40 refs.

Research and Observations on the Importance and Meaning of the Waaler-Rose Reaction in Rheumatology. (Ricerche ed osservazioni sull'importanza e sul significato della reazione di Waaler-Rose in reumatologia.) DANEO, V., and EINAUDI, G. (1954). *Minerva med.* (*Torino*), **45**, 714. 36 refs.

ACTH, Cortisone, and Other Steroids

Influence of Protein Metabolism on Bacterial Allergy. Its Relation to Cortisone Desensitization. LONG, D. A. (1954). *Lancet*, **1**, 231. 4 figs, 18 refs.

It has been shown that ascorbic acid depresses the sensitivity to tuberculin (as measured by the size of the skin reaction) of guinea-pigs injected with B.C.G., and that this desensitizing action is antagonized by a factor present in cabbage which apparently prevents the oxidation of ascorbic acid to dehydroascorbic acid; this factor is in turn antagonized by cortisone, which thus permits the decrease in sensitivity brought about by ascorbic acid to take place. Further experiments carried out at the National Institute for Medical Research, London, have shown that skimmed milk has properties similar to those of cabbage, as also has methionine, which is present in both. On the other hand ethionine, an antimetabolite to methionine, antagonizes the action of cabbage and skimmed milk in the same way as cortisone. The "cabbage factor" and the similar factor present in skimmed milk are therefore thought to be probably identical with methionine.

By analogy with the action of alloxan in diabetes, the author presents the hypothesis that cortisone depresses sensitivity to tuberculin in the guinea-pig by interfering with the anabolism of glutathione. The resulting fall in glutathione concentration in the tissues would increase the oxidation of ascorbic acid to dehydroascorbic acid, which inactivates phosphoglucomutase, resulting in an increase in the tissue concentration of glucose-1-phosphate, which has a desensitizing influence.

H. Herxheimer.

Enhancement of the Ascorbic Acid Depleting Activity of ACTH by Polyphloretinphosphate. [In English.] WEIDMANN, H. (1953). *Acta endocr.* (*Kbh.*), **13**, 287. 2 figs, 3 refs.

It has been shown that the effect of a dose of ACTH (corticotrophin) on the ascorbic acid content of the rat's adrenal glands is prolonged and enhanced if the ACTH is given together with polyphloretin phosphate, an effect which has been attributed to the anti-enzymatic properties of the latter compound. To test this assumption the author has compared the effect obtained when ACTH and polyphloretin phosphate were given separately with that obtained when the two substances were incorporated in one injection.

Male rats were subjected to hypophysectomy and, on the following day, to unilateral adrenalectomy. The drug or drugs were then given, and ½ to 24 hrs later the remaining adrenal gland was removed, the two glands being separately weighed and their ascorbic acid content assayed. Four groups of rats were treated as follows:

(1) ACTH alone (0·1 unit/100 g. body weight);
(2) ACTH+polyphloretin phosphate (2 mg./100 g.) as a freeze-dried complex dissolved in saline;
(3) ACTH and polyphloretin phosphate given as separate intramuscular injections;
(4) ACTH parenterally and polyphloretin phosphate (10 mg./100 g.) by mouth.

It was found that the enhancement of activity of the ACTH was quantitatively the same however the polyphloretin phosphate was given, though the substance itself had no effect on the adrenal ascorbic acid content either in hypophysectomized or in intact rats. These results are held to indicate that polyphloretin phosphate protects ACTH from inactivation in the tissues. Whether the mechanism of this action is anti-enzymatic in nature is not indicated by these experiments, but this seems the most likely explanation. *Nancy Gough.*

Effect of Large Doses of Cortisone upon the Ability of the Reticuloendothelial Cells to phagocytose Streptococci. CLAWSON, B. J., and NERENBERG, S. T. (1953). *J. Lab. clin. Med.*, **42**, 746. 15 refs.

The efficiency of the reticuloendothelial cells (Kupffer's cells) to engulf bacteria appears to be about equal in the rats treated with large doses of cortisone and in normal rats, but the ability of these cells in the treated animals to destroy the engulfed organisms is definitely depressed. This depression of the reticuloendothelial cells may be an important factor in the increased susceptibility to infection in animals treated with large doses of cortisone.—[*Authors' summary.*]

Effect of Cortisone upon the Therapeutic Efficacy of Antibiotics. JAWETZ, E., and MERRILL, E. R. (1953). *Science*, **118**, 549. 6 refs.

Cortisone is known to aggravate various infections in man and animals, probably by depressing the host's defence mechanisms. In the present study, undertaken at the University of California School of Medicine, San Francisco, in order to determine whether this action of cortisone might impair the therapeutic efficacy of antibiotics, groups of white mice were infected with *Klebsiella pneumoniae* and subsequently treated by the injection of either streptomycin or aureomycin for 3 days.

In the groups of animals which also received cortisone treatment, starting 24 hrs before infection, the cure rates were usually lower than in those not given cortisone. The impairment was most apparent when the dose of antibiotic was barely curative when given alone; for example, 2 mg. aureomycin reduced the mortality from 100 per cent. to 12 per cent., but when 1 mg. cortisone and 2 mg. aureomycin were given the mortality was 72 per cent. If sufficient antibiotic was injected, however, the cure rate was not reduced by the administration of cortisone at the same time. These findings, which were

equally true of the bacteriostatic drug, aureomycin, and of the bactericidal drug, streptomycin, are in keeping with the view that the host's defence mechanisms contribute materially to the curative action of antibiotics, and that these mechanisms are depressed by the action of cortisone.

Derek R. Wood.

Ascorbic-Acid Metabolism after Administration of Corticotrophin. McSwiney, R. R., Clayton, B. E., and Prunty, F. T. G. (1954). *Lancet*, **1**, 178. 5 figs, 17 refs.

The disappearance of ascorbic acid from the adrenal cortex on injection of corticotrophin (ACTH) has been noted by a number of workers in several different species of animals. But whether the ascorbic acid is consumed within the cortex or extruded into the plasma has never been clearly demonstrated. At St. Thomas's Hospital, London, therefore, the authors investigated the changes in the quantity of reduced ascorbic acid and its immediate oxidation products in the plasma and urine of patients treated with ACTH and in the urine of guinea-pigs given injections of the hormone.

The reduced ascorbic acid value was determined by titration with dichlorophenolindophenol; direct determination was made in the case of plasma, but for urine, which contains interfering substances, the "formaldehyde correction" procedure developed by Snow and Zilva (*Biochem. J.*, 1944, **38**, 458) was followed. The amounts of the immediate oxidation products of ascorbic acid, namely, dehydro-ascorbic acid and diketogulonic acid, were also determined, the former by reduction with hydrogen sulphide and the latter by the method of Roe and Kuether (*J. biol. Chem.*, 1943, **147**, 399).

Six patients receiving treatment with ACTH were studied. All were given a diet containing no more than 40 mg. of ascorbic acid per day, which was supplemented in two cases by 300 mg. per day and in one case by 30 mg. per day. After a stabilization period and before administration of ACTH, two of the patients were found to have a high initial ascorbic acid level in the plasma (greater than 1 mg. per 100 ml.), two had an intermediate initial level (0·75 to 1·0 mg. per 100 ml.), and two a low initial level (less than 0·6 mg. per 100 ml.). The patients with high and intermediate initial levels responded similarly to administration of ACTH, showing increased output of ascorbic acid in the urine for the first 2 or 3 days only; the dehydro-ascorbic acid output was also increased in one case but not in the others. Plasma determinations showed a tendency for the levels of oxidation products of ascorbic acid to rise at first and then fall with continued therapy. The findings in guinea-pigs with adequate intake of ascorbic acid were similar. Patients with low ascorbic acid saturation did not, however, show these changes.

Three possible mechanisms are suggested and discussed, namely, increased renal clearance of ascorbic acid, a passive shift of ascorbic acid from cells to extracellular fluid with the usual shift of water, and a further transfer of ascorbic acid in the same direction due to some unidentified mechanism. *Nancy Gough.*

Action of Pituitary Somatotrophin in the Prevention of Infections Favoured by Overdosage of Cortisone. (Sur l'action de la somatotrophine hypophysaire dans la prévention des infections favorisées par le surdosage en cortisone.) Ducommum, P., and Ducommum, S. (1953). *Ann. Endocr.* (*Paris*), **14**, 765. 1 fig., 7 refs.

In order to confirm the finding of Selye (*Canad. med. Ass. J.*, 1951, **64**, 489; *Abstracts of World Medicine*, 1951, **10**, 523) that pituitary somatotrophic hormone can counteract the development of lowered resistance to infection caused by overdosage with ACTH and cortisone, the authors, working at the Institute of Experimental Medicine and Surgery, University of Montreal, carried out four experiments on rats the results of which are here described.

In the first experiment, it was shown that the development of bacterial infection and the mortality from such infection were clearly promoted by the administration of cortisone in doses of about 20 mg. daily; and that this effect of cortisone could be counteracted by the simultaneous administration of pituitary growth hormone. In the second, it was shown that growth hormone had no effect on connective tissue, as measured by the rate of migration of subcutaneously injected haemoglobin. In the third, it was established, mainly by observations of changes in body weight of the animals, that the protective effect of growth hormone was not part of its general anabolic properties. In the fourth experiment, they showed that growth hormone was less able to prevent infection in adrenalectomized rats. Finally, it was established that neither testosterone propionate, deoxycortone acetate, nor oestradiol possessed the "anti-infection" properties of growth hormone. *B. Nordin.*

Effects of Administration of Hydrocortisone and Somatotrophic Hormone. (Sur les effets de l'administration de l'hydrocortisone et de l'hormone somatotrope.) Horava, A., and Selye, H. (1953). *Ann. Endocr.* (*Paris*), **14**, 772. 1 fig., 5 refs.

In this study of the nephrosclerosing action of hydrocortisone, alone and in combination with pituitary somatotrophic hormone, carried out at the University of Montreal, 24 male rats were divided into four groups. The first group acted as a control, the second received 2·5 mg. of hydrocortisone subcutaneously daily, to the third pituitary growth hormone was given three times daily subcutaneously, and the fourth group received both substances. At the end of 3 weeks the animals were killed and examined.

It was confirmed that hydrocortisone produced severe loss of weight, atrophy of the adrenal and thymus glands and of the spleen, mild glomerular lesions, slight elevation of the blood pressure, and necrotic foci in the lungs. Growth hormone did not prevent the adrenal and thymic atrophy and it aggravated the renal lesions, but it did prevent the appearance of infected foci in the lungs and also the severe loss of weight. The possible mechanism of this action is discussed and several hypotheses are proposed. *B. Nordin.*

Prolonged Cortisone Therapy in the Congenital Adrenocortical Syndrome. (Die Cortisondauerbehandlung des kongenitalen adrenogenitalen Syndroms.) PRADER, A. (1953). *Helv. paediat. acta*, **8**, 386. 14 figs, 46 refs.

The author reports the results of the treatment with cortisone of ten female and four male patients with congenital adrenocortical hyperplasia. The ages of the females ranged from 3 to 30 years, and of the males from 6 to 36. Six of the former had undergone unilateral adrenalectomy without improvement, followed by oestradiol implantation in doses ranging from 40 to 280 mg.; six (four of them under 14) had undergone amputation of the enlarged clitoris; and three had received a short course of cortisone some time previously.

All fourteen patients were treated with cortisone for periods of 3 to 20 months (average 13 months). The drug was given by mouth in three doses totalling 25 to 75 mg. daily, intramuscularly in doses averaging 75 mg. every fourth day, or in the form of "depot-cortisone", a long-acting suspension of cortisone crystals up to 100 μ in size, of which a single injection of 600 to 800 mg. was given monthly. The clinical effects were identical with all three methods of administration, and there were no side-effects in the two cases treated with depot-cortisone. The dosage was adjusted to that which kept the urinary excretion of 17-ketosteroids just below 8 mg. daily in the older patients, and which caused minimal inhibition of growth in the younger patients. Some of the patients were admitted to hospital for the first 2 or 3 weeks, but for the most part treatment was given at home, the patients sending urine for 17-ketosteroid estimations and attending as out-patients every 2 or 3 months. Sodium intake was not restricted and no extra potassium was given.

The treatment was uniformly successful, the main results being as follows:

(1) acne disappeared within a few weeks;

(2) within 1 to 3 months the older girls became more feminine in appearance and their breasts developed;

(3) the testicles of the older boys began to mature and testicular tumours became smaller;

(4) hirsuties regressed in the older girls and did not develop in the younger children;

(5) the pitch of the voice rose in the older girls;

(6) marked pigmentation disappeared;

(7) increased rate of growth and of skeletal development in the younger children was prevented;

(8) the haemoglobin value, if increased, became normal;

(9) the psychological effects of the glandular disturbance were improved;

(10) menarche occurred, usually within 7 months.

No untoward side-effects were seen, even after 20 months' treatment. When treatment was stopped, however, recurrence of symptoms was the rule. The author recommends that treatment be started early in childhood and continued for years, strict supervision in regard to 17-ketosteroid excretion, blood pressure, growth, and weight being essential. With older patients, the desirability of treatment must be decided on its merits in each case. *V. C. Medvei.*

Cortisone in the Treatment of Chronic Adrenal Insufficiency. FOURMAN, P., and HORLER, A. R. (1954). *Lancet*, **1**, 334. 32 refs.

The results achieved with cortisone in the treatment and maintenance of eight patients with Addison's disease and three with hypopituitarism, who were followed up at the Radcliffe Infirmary, Oxford, over a period of 18 months, are briefly summarized. Most of the patients with Addison's disease had received deoxycortone acetate and salt previously, and the addition of cortisone usually resulted in the dosage of the former being halved. For maintenance, 10 to 25 mg. cortisone was given daily in four divided doses, but much larger amounts were required during crises. In most cases appetite improved and the patient experienced a sense of well-being and an increase in initiative and vigour. In six of the patients with Addison's disease there were healed or active tuberculous lesions but cortisone did not appear to affect this condition. *A. C. Crooke.*

Adrenal Response to Corticotrophin. Effect of ACTH on Plasma Adrenal Steroid Levels. BAYLISS, R. I. S., and STEINBECK, A. W. (1954). *Brit. med. J.*, **1**, 486. 3 figs, 13 refs.

The authors, working at the Postgraduate Medical School of London, have assessed the response of the adrenal glands to stimulation by ACTH (corticotrophin) given by various routes by measuring the changes produced in the plasma content of 17 : 21-dihydroxy-20-ketosteroids (such as hydrocortisone, cortisone, and their metabolic reduction products). The method of assay used by the authors has been described elsewhere (*Biochem. J.*, 1953, **54**, 523).

The drug was administered by intravenous infusion to twelve subjects, only two of whom "were not clinically ill at the time of study", the remainder suffering from a variety of diseases. An increase in the plasma steroid level appeared within 15 to 30 min. of starting the infusion, the level reaching its maximum in most cases after one hour, remaining fairly constant during the infusion, and falling rapidly after its completion. A maximal response was obtained in most cases with a dose of one unit ACTH per hour for 6 to 8 hours, the plasma steroid level rising to between 24 and 36 μg. per 100 ml. After repeated daily infusions in two cases a higher level was obtained suggesting that repeated stimulation of the adrenal cortex increases its hormone output. A single intramuscular injection of 80 units ACTH in gelatin ("acthar" gel) was given to seventeen patients, "all of whom were comfortable at the time of study, except three with asthma". The plasma steroid level began to rise within 2 hrs and reached its maximum between 4 and 8 hrs after the injection, falling to normal in most cases within 12 to 24 hrs. Injections of 20 units ACTH in acthar gel produced a more transient elevation of the plasma steroid level, although in some cases the maximum level reached did not differ significantly from that obtained with 80 units. In five cases in which repeated injections of acthar gel were given there was again a progressively increasing response.

A single intramuscular injection of ACTH dissolved in

saline was given to sixteen patients, eight of whom were "clinically ill", the maximum response being obtained after 1 to 2 hrs and the effect of the injection passing off within 4 to 6 hrs. The degree of response was very variable, however, and in two cases was negligible.

It is concluded that intravenous infusion is probably the most reliable, and certainly the most economical, method of administration of ACTH. *Nigel Compston.*

Action of Cortisone on Transplanted and Induced Tumors in Mice. BASERGA, R., and SHUBIK, P. (1954). *Cancer Res.*, **14**, 12. 6 figs, 28 refs.

The action of cortisone has been studied on the heterologous transplantation, growth, and metastatic diffusion of a transplantable adenocarcinoma in DBA mice, and on the genesis, growth, and metastatic diffusion of tumors induced in the skin and subcutaneous tissues of Swiss mice with methylcholanthrene. Cortisone did not show any appreciable influence on the heterologous transplantation of a mammary adenocarcinoma from DBA mice and on the growth of methylcholanthrene-induced tumors in Swiss mice. The growth rate of a transplanted adenocarcinoma in DBA mice was temporarily inhibited by the administration of cortisone. The induction of skin tumors in Swiss mice by methylcholanthrene has been markedly inhibited by the administration of 0·5 mg. of cortisone daily. Cortisone has been found to favor an increased metastatic spread of all the experimental tumors studied.—[*Authors' summary.*]

ACTH and Cortisone in the Treatment of Keloids. RONCHESE, F., and KERN, A. B. (1954). *New Engl. J. Med.*, **250**, 238. 3 figs, 6 refs.

ACTH and cortisone were tried at Rhode Island Hospital, Providence, in the treatment of five cases of keloid formation. A female aged 17 had undergone bilateral mastoidectomy at the age of 4, after which keloids formed behind both ears. Radiotherapy was given and later the keloids were excised. When she was seen some years later a large keloid was observed on each of the original sites. She was given an intramuscular injection of 25 mg. ACTH, the keloids were excised, and ACTH in a dose of 20 mg. was injected 6-hrly thereafter. The result was satisfactory, only a very small tumour reappearing behind the left ear. Keloids on the abdomen and knee were unaffected. A woman aged 28 had keloids on the chest on the site of old acne lesions; these recurred after excision and radiotherapy. She was given 25 mg. cortisone by mouth three times a day for 3 weeks, and cortisone ointment containing 16·6 mg./g. was applied for a month. She complained of pain and irritation in the scars; the keloids reformed, and during the following 3 months they increased in size and symptoms became more severe. In two cases keloids appeared where the lobes of the ears had been pierced. In one of these patients, a girl aged 14, they were excised and cortisone ointment was applied for 2 months, but the keloids reformed. In the fifth case in the series a keloid appeared at the site of an injury to the neck of a girl aged 11. It was excised and cortisone ointment applied, but the growth recurred.

The authors conclude that surgery with radiotherapy remains the treatment of choice in this condition.

E. Lipman Cohen.

Mode of Action of Sodium Pyrocatecholcarboxylate and Sodium Diacetylpyrocatecholcarboxylate and of their Synergism with Cortisone in the Rat. (Étude du mode d'action du pyrocatechol carboxylate de soude et du diacetyl pyrocatechol carboxylate de soude et de la synergie cortisone pyrocatechol carboxylate de soude chez le rat.) MICHOTTE, L. J., LEVIS, S., and DAUBY, J. (1953). *Rev. Rhum.*, **20**, 743. 1 fig., 12 refs.

This paper from l'Union Chimique Belge describes work designed to throw light on the mode of action of sodium pyrocatechol carboxylate and its diacetyl derivative. The authors have compared the effects of these compounds with that of sodium salicylate, cortisone acetate, and ACTH when injected into intact rats, hypophysectomized rats, and adrenalectomized rats, in doses which produce a marked eosinopenia in intact rats. The eosinophils were counted before and after the administration of the test substances, the intact rats being given Nembutal so that no stress-reaction should interfere. These experiments showed that the eosinopenia produced by sodium pyrocatechol-carboxylate and its derivative was not dependent on the presence of either the hypophysis or the suprarenal gland. Furthermore, these compounds had no effect on the adrenal ascorbic acid and had no power to prolong the survival time of rats exposed to cold-stress.

Epinephrine, which also produces a fall in the blood eosinophils in adrenalectomized rats, seemed to react synergistically with cortisone; that is, doses of epinephrine and cortisone, each too small to produce eosinopenia alone, caused a significant fall if administered together. In the same way, sodium pyrocatecholcarboxylate and its diacetyl derivative show synergism with cortisone, so that a dose one-quarter the minimum active amount of cortisone can produce eosinopenia and protection against cold-stress in the adrenalectomized rat. Hence sodium pyrocatecholcarboxylate can replace epinephrine in the physiological complex cortisone-epinephrine.

Nancy Gough.

Treatment of Periarthritis of the Shoulder with Hydrocortisone Acetate. (Le traitement de la périarthrite de l'épaule par l'hydrocortisone acétate.) ROBECCHI, A., and CAPRA, R. (1953). *Rev. Rhum.*, **20**, 757.

After commenting on the great variety of treatments which have been advocated for periarthritis of the shoulder the authors maintain that whereas cortisone gives results which are in no way superior to simpler, cheaper, and less dangerous forms of therapy, hydrocortisone on the other hand gives excellent results on local injection and is the treatment of choice. Of fifty cases so treated at the Turin Rheumatological Centre, in twenty (58 injections) the condition was acute, in fourteen (38 injections) the condition was chronic but without fixation of the joint, and in sixteen (58 injections) the joint was more or less "frozen". Hydrocortisone was injected, so far as possible, into the region of affected

tendons or of the subacromial bursa, but in a few intractable cases it was given intra-articularly. The usual dosage was 25 mg. (1 ml.), and an interval of 3 to 5 days was allowed between injections.

The best results were obtained in acute cases, where rapid relief from pain was experienced in all but one case, the final result being classified as "good" or "very good" in sixteen out of twenty. A similar degree of relief of pain was obtained in seven out of the fourteen chronic non-rigid cases, and in seven out of the sixteen cases with rigidity. Stiffness and immobility, however, appeared to be uninfluenced and required physical methods of treatment, which the relief of pain greatly facilitated. There was some evidence that calcification, when present, was more rapidly absorbed after treatment with hydrocortisone than is usually the case in spontaneous remissions. In the opinion of the authors, the radio-opaque appearances in such cases are due to subacromial bursitis, the fluid being rich in calcium salts. *D. Preiskel.*

Locally-Administered Hydrocortisone in the Rheumatic Diseases. A Summary of its Use in 547 Patients. BROWN, E. M., FRAIN, J. B., UDELL, L., and HOLLANDER, J. L. (1953). *Amer. J. Med.*, **15**, 656. 1 fig., 19 refs.

Over a period of 18 months at the Hospital of the University of Pennsylvania, Philadelphia, 547 patients with rheumatic disease received injections of hydrocortisone into inflamed joints or bursae, the total number of injections being 3,757. Of the 547 patients, 249 had rheumatoid arthritis, 231 had osteo-arthritis, eighteen had gout, and 49 had various rheumatic conditions (details given).

The dose of hydrocortisone ranged from 5 to 50 mg. according to the size of the joint and the result obtained. Results were assessed both symptomatically and by the size and range of movement of the joint. Many of the patients with rheumatoid arthritis were receiving systemic treatment (cortisone or gold, or both) so that the results were difficult to assess, but it is considered that "satisfactory improvement" occurred in 85 per cent. of patients treated. Those with osteo-arthritis of the hip were noticeably resistant to treatment, possibly because of the technical difficulty of injection into this joint. Reactions, which occurred after 2·3 per cent. of the injections, included transient local exacerbation of inflammation, weakness of a limb, general malaise, urticaria, and in one case infection of the joint.

It is concluded that intra-articular injection of hydrocortisone is a useful adjuvant in the general treatment of rheumatoid arthritis, osteo-arthritis, gout, and various local rheumatic disorders. *Kathleen M. Lawther.*

Effect of Cortisone and Corticotropin on the Prognosis of Systemic Lupus Erythematosus. Survey of 83 Patients with Positive Plasma L.E. Tests. HASERICK, J. R. (1953). *Arch. Derm. Syph.* (*Chicago*), **68**, 714. 16 refs.

The author describes the natural course of systemic lupus erythematosus in 83 patients seen at the Cleveland Clinic, Cleveland, Ohio, and assesses the results of treatment with cortisone or corticotrophin (steroid therapy) in 73. The series included only those cases in which the L.E. phenomenon was present. The author gives reasons for preferring the L.E.-plasma test to the L.E.-cell test; he considers that the former is as specific in the diagnosis of systemic lupus erythematosus as the Wassermann test is in the diagnosis of syphilis. He points out that before the introduction of the L.E.-plasma test a diagnosis of systemic lupus erythematosus was made only in typical, severe cases. Since then milder, atypical forms of the disease have been recognized, and when these are included in any series of cases the over-all prognosis is improved. A comparison of statistics of cases diagnosed by the L.E.-plasma test with those of cases diagnosed clinically is therefore invalid.

The course of lupus erythematosus in ten patients treated before steroid therapy was available is compared with that in 73 given cortisone or corticotrophin [details of the immediate and maintenance dosage are not given]. The author's criterion of effective therapy is the survival of those patients "considered to have imminently fatal systemic lupus erythematosus". Only one of the ten untreated patients was alive 5 years after the onset of the severe phase; the remainder died one month to one year after onset. Of the treated patients, 44 were expected to die and steroid therapy is considered to have prevented death in thirty of these. A number of deaths occurred within a few days of the start of treatment. In four cases renal failure was progressive in spite of treatment. Of eleven patients given steroid therapy in 1949 and 1950, seven were alive in 1953. Not only was life prolonged by these drugs, but morbidity was reduced.

In the discussion which followed, the author discussed the false positive response to the L.E.-plasma test, which is sometimes noted in patients reacting to penicillin. Such patients were "very low-grade positive", only a small number of cells undergoing the characteristic changes. In systemic lupus erythematosus the reactions were always strongly positive. *Nigel Compston.*

Treatment of Pemphigus with Cortisone by Mouth. CONRAD, A. H., GREENHOUSE, J., and WEISS, R. S. (1954). *Arch. Derm. Syph.* (*Chicago*), **69**, 66. 1 ref.

The authors describe in some detail the effects of treatment with cortisone by mouth in five cases of pemphigus vulgaris, two of pemphigus erythematosus (Senear-Usher syndrome), and one of pemphigus foliaceus, giving the laboratory findings. Cortisone controlled or cleared the eruption in all cases except that of pemphigus foliaceus. Large doses (in one case 900 mg. a day) were given, and in one case of pemphigus vulgaris the cortisone was supplemented by heparin-sodium and later by nitrogen mustard. One patient, a man aged 43, whose skin had cleared completely with a dose of 600 mg. cortisone daily, later relapsed and died despite the resumption of treatment. ACTH (corticotrophin) produced no response in the three cases in which it was tried.

[Beyond the statement that "the patient must be followed indefinitely and supportive treatment with the drug given" no details of maintenance dosage are given.] *J. E. M. Wigley.*

Treatment of Blood Disorders with ACTH and Cortisone. PANEL OF THE MEDICAL RESEARCH COUNCIL ON THE HAEMATOLOGICAL APPLICATIONS OF ACTH AND CORTISONE (1953). *Brit. med. J.*, **2**, 1400. 3 refs.

The results of administration of ACTH or cortisone to 65 patients with haematological disorders are summarized. The daily dosage varied from 80 to 100 mg. ACTH and from 100 to 300 mg. cortisone. Most patients were treated for 2 to 3 weeks, the total dosage varying from 1,000 to 3,000 mg. ACTH and from 1,000 to 7,000 mg. cortisone. A "complete" response was defined as one in which the clinical condition of the patient and the haematological findings "returned approximately to normal", and a "partial" response as one in which "there was improvement of lesser extent".

Three out of ten patients suffering from idiopathic or secondary acquired haemolytic anaemia responded partially and five responded completely. The reaction to the antiglobulin (Coombs) test was negative in three patients, including the two who failed to respond. Treatment was given to 22 patients with purpura. Of fifteen with idiopathic thrombocytopenic purpura, ten responded favourably, but in five out of six patients with non-thrombocytopenic purpura treatment was ineffective. Of 24 patients with acute leukaemia of various types or reticulosis only five responded, the response being complete in two.

The effect of the hormones on other haematological disorders (nine cases) is briefly mentioned. The paper also contains the results of a follow-up examination of 88 patients given ACTH or cortisone in 1951 (*Brit. med. J.*, 1952, **1**, 1261; *Abstracts of World Medicine*, 1952, **12**, 428).

It is concluded that the best results are likely to be obtained in cases of acquired haemolytic anaemia and of idiopathic thrombocytopenic purpura, but that as the response is usually temporary, treatment over many months may be necessary. *J. V. Dacie.*

Effect of *para*-Aminobenzoic Acid on the Metabolism of Cortisone in Liver Tissue. WIESEL, L. L. (1954). *Amer. J. med. Sci.*, **227**, 80. 8 refs.

Studies of the metabolism of cortisone in slices of rat and human liver have confirmed the author's previously published conclusion that *para*-aminobenzoic acid interferes with the inactivation of cortisone by liver tissue. It interferes markedly with the rapid reduction of the unsaturated conjugated system of the cortisone molecule, while permitting more rapid degradation of the side-chain. *W. S. C. Copeman.*

Infants of Diabetic Mothers with special reference to Neonatal Adrenocortical Function as assessed by Urinary Excretion of Corticoids and Tests using Adrenocorticotrophic Hormones. [In English.] BJÖRKLUND, S. I. (1954). *Acta endocr.* (*Kbh.*), **15**, 25. 19 refs.

The author, working at the Flensburg Children's Hospital, Malmö, Sweden, has investigated the adrenocortical activity of newborn infants of diabetic mothers [with some interesting results].

In all, seven such infants were studied between the first and 14th day of life, and three infants of non-diabetic mothers acted as controls. Where possible, 24-hr specimens of urine were used for corticoid estimation, and up to six such estimations were performed in each case. The eosinopenic response to 5 mg. ACTH was also assessed in five of the cases, eosinophil counts being made before and 6 hrs after administration of corticotrophin. The urinary corticoids present were thought to represent 11-oxycorticosteroids and 11-deoxycorticosteroids, together with other as yet unrecognized corticoids.

The results, which were expressed in mg. per sq. metre of body surface, and in μg. per kg. body weight, showed that there was a significant increase in urinary corticoid excretion in six of the seven infants as compared with the control subjects and with the values for normal infants published by other workers. Four of the five infants were thought to show a significant eosinopenia following administration of ACTH. It was also shown that the urinary excretion of corticoids fell progressively from the initial high figure.

The author offers the intriguing suggestion that this increase in 11-oxycorticosteroids offsets the hyperinsulin supposedly present in infants of diabetic mothers, as judged by the finding of pancreatic islet-cell hyperplasia. He also assumes that the high birth-weight, Cushing-like appearance, and oedema, all of which were lost rapidly in the first week, are due to the over-production of corticoids, which, however, tends to correct itself within the first week of life. He claims to have shown by electrocardiography that there is also evidence of hypokalaemia in such infants, and suggests that the administration of potassium salts might usefully be added to the usual treatment of these cases.

[This would appear to be an important paper, and further observations with larger numbers would be valuable. Figures for the eosinophil counts following administration of ACTH are rather borderline in all except two of the cases.] *J. N. Harris-Jones.*

Treatment of Herpes Zoster with Cortisone. GELFAND, M. L. (1954). *J. Amer. med. Ass.*, **154**, 911. 9 refs.

An account of five cases treated with systemic cortisone, two of which had ocular complications for which local cortisone was given. Dramatic relief of pain, a shortened course of the disease, and absence of post-herpetic neuralgia are claimed. *H. E. Hobbs.*

Local Use of Cortisone in Different Ocular Diseases. [In Serbo-Croat.] LUKIĆ, D., MILOŠEVIĆ, B., and KECMANOVIĆ, Z. (1954). *Srpski Arhiv*, **82**, 202.

After a brief survey of the medical literature the authors give the results in 241 patients with various ocular diseases treated with local cortisone, usually by the subconjunctival route. The conclusions are:

(1) In affections of the eye with effusion or inflammation, the result is favourable.

(2) Local application is preferable to parenteral use because it does not provoke a general reaction and may be used in cases where general treatment is contra-

indicated. Besides the absence of reaction, good tolerance and minimal doses are very important. It may also be used with out-patients.

(3) Subconjunctival injections are especially effective in affections of the anterior segment, whereas the introduction of cortisone to the anterior chamber should be reserved for serious cases of iridocyclitis. Retrobulbar injections and general treatment with cortisone or ACTH should be given in affections of the posterior segment of the eye as well as in cases where local use has not been satisfactory.

(4) Treatment should be initiated as early as possible and duration varies individually. Discontinuation of cortisone in some cases provokes a recurrence.

(5) Treatment with cortisone is symptomatic and auxiliary and should be combined with causal treatment in order to achieve a lasting effect and to avoid recurrence. *D. Lukić.*

Hydrocortisone in Ophthalmology. GORDON, D. M. (1954). *Amer. J. Ophthal.*, **37**, 533.

Topical applications of hydrocortisone have proved superior to cortisone and subconjunctivally it may be effective where cortisone has failed. These conclusions are based on an analysis of the treatment of 152 cases. The acetate salt of hydrocortisone was inferior to the free-alcohol form when administered subconjunctivally. For lesions of the posterior segment of the eye an initial course of systemic therapy is followed by subconjunctival and then topical therapy. *S. J. H. Miller.*

Cortisone in Pneumoconiosis with and without Reversible Bronchoconstriction. KENNEDY, M. C. S. (1954). *Lancet*, **1**, 77. 17 refs.

At the Medical Research Council Silicosis Treatment Centre, Stoke-on-Trent, twelve patients with chronic lung disease, all but two of whom had radiological signs of pneumoconiosis, were observed before, during, and after treatment with 100 mg. cortisone acetate daily by mouth for 14 days. Estimates of the maximum ventilatory capacity were made by measuring the expiration flow rate (E.F.R.); seven patients whose E.F.R. increased by more than 10 per cent. after inhalation of 1 : 1,000 adrenaline were considered to have "reversible bronchoconstriction".

Although eight of the twelve patients claimed subjective improvement of dyspnoea during and after cortisone therapy, the mean E.F.R. of the group both before and after adrenaline inhalation was unchanged. There was a slight but not significant fall in the mean erythrocyte sedimentation rate of the group at the end of the treatment. No radiological changes were seen and there was no evidence of activation of tuberculosis.

It is concluded that cortisone has no place in the treatment of bronchospasm in pneumoconiosis.

C. M. Fletcher.

Influence of Cortisone on Induced Asthma and Bronchial Hyposensitization. HERXHEIMER, H. (1954). *Brit. med. J.*, **1**, 184. 9 refs.

An investigation was carried out at University College Hospital, London, to determine whether cortisone would influence an induced asthmatic attack. Asthma was induced by allowing the patient to inhale the appropriate allergen, and the intensity of the attack was judged by the time taken to induce it and the reduction in the vital capacity. Of eleven patients tested, five reacted "immediately"—that is, 2 to 10 min. after exposure; the remaining six were "late reactors"—that is, the asthmatic attack occurred 7 to 16 hrs after exposure. The patients were given cortisone, and when under its influence were exposed to double or treble the amount of allergen which had previously caused a mild attack of asthma. This exposure was repeated after the dose of cortisone was reduced and after administration of the drug ceased. It was found that after all three exposures to the allergen, the asthmatic attack in the immediate reactors was mild and transient; in the late reactors no asthmatic attack was produced. It is concluded that cortisone abolishes or modifies the violence of the reaction to an overdose of allergen, and prevents hypersensitization while permitting the development of hyposensitization. *A. W. Frankland.*

Treatment of Dystrophia Myotonica with ACTH. GARAI, O. (1954). *J. Neurol. Neurosurg. Psychiat.*, **17**, 83. 5 refs.

The author describes the results obtained at King's College Hospital, London, with ACTH in the treatment of four patients suffering from dystrophia myotonica. The myotonia was somewhat relieved, but in those cases in which wasting and dystrophy of the muscles were prominent features ACTH had little noticeable effect. This drug was preferred to cortisone because in previously reported cases the latter had proved of little value. The possible mode of action of ACTH on myotonia is discussed in relation to its effect on the potassium content of muscle. *J. B. Stanton.*

Corticotrophin Zinc Phosphate and Hydroxide. Long-acting Aqueous Preparations. HOMAN, J. D. H., OVERBEEK, G. A., NEUTELINGS, J. P. J., BOOIJ, C. J., and VAN DER VIES, J. (1954). *Lancet*, **1**, 541. 1 fig., 20 refs.

Corticotrophin Zinc Phosphate. A Long-acting Aqueous Preparation. GREENE, R., and VAUGHAN-MORGAN, J. (1954). *Lancet*, **1**, 543. 2 figs, 4 refs.

Corticotrophin Zinc Phosphate. A Long-acting Aqueous Preparation. FERRIMAN, D. G., ANDERSON, A. B., and TURNER, P. P. (1954). *Lancet*, **1**, 545. 1 fig., 3 refs.

Corticotrophin Zinc Phosphate. A Long-acting Aqueous Preparation. DEN OUDSTEN, S. A., VAN LEEUWEN, L., and COERS, R. J. (1954). *Lancet*, **1**, 547. 4 figs, 4 refs.

The adsorption of an active drug on to a flocculent precipitate is a standard means of concentrating it and prolonging its period of effective action on injection. This technique has now been applied to corticotrophin (ACTH) since to obtain prolonged action from a single injection would be an advantage both clinically and economically, although concentration is not an important problem. These four papers deal with the adsorption product of corticotrophin and zinc phosphate.

In the experiments reported by Homan and others, the

combined product was shown to have an effect on the liver glycogen content of hypophysectomized rats greater than that of the same amount of ordinary corticotrophin in aqueous solution given in hourly doses over the same period (8 hours), while the reduction in weight of the thymus was equivalent to that produced by doses of the aqueous solution 10 to 32 times greater. Inactivation of ordinary corticotrophin by serum enzymes *in vitro* was considerable, but protection from enzymatic destruction and good stability was evident in the zinc suspensions in the presence of serum. A solution of 20 units corticotrophin and 1 to 2 mg. zinc chloride per ml. at *p*H 3·0 showed excellent stability on storage, and for clinical or biological use it was precipitated with trisodium phosphate and a final *p*H of 6·5 obtained by the addition of sodium hydroxide. Precipitation immediately before clinical use obviated crystallization in the flocculent suspension.

The effect of the combination of corticotrophin with zinc phosphate was compared with that of aqueous corticotrophin in six cases of rheumatoid arthritis by Greene and Vaughan-Morgan, the degree of amelioration of symptoms and increase in the urinary excretion of 17-ketosteroids (total neutral fraction) produced by each preparation being assessed. The effect of the combination of the symptoms was, in all but one case, better than that of ordinary corticotrophin, and was more lasting in four cases, the lack of superiority of the zinc preparation in the other two cases being attributed to an unusually prolonged effect of ordinary corticotrophin. The symptomatic effect of each injection of 20 units of the combination lasted 2 days or more, but better results were obtained by giving daily injections of 10-20 units. The 17-ketosteroid output was usually more than double that produced by ordinary corticotrophin in a similar dosage.

Ferriman and others compared the clinical effects of the corticotrophin-zinc-phosphate preparation and an "ethyl-oleate-beeswax preparation of corticotrophin" in seven cases of rheumatoid arthritis and one of ankylosing spondylitis. The latter preparation was never effective for more than 24 hrs, whereas the effect of the former lasted 24 to 48 hrs. Treatment with the zinc phosphate preparation resulted in a constant and persistent decrease in the eosinophil count and an increase in 17-ketosteroid excretion, whereas the effect of the ethyl oleate preparation was variable, although more constant than with ordinary corticotrophin.

Corticotrophin zinc phosphate was used by den Oudsten and others in 25 cases of rheumatoid arthritis. Although the therapeutic effect did not differ essentially from that obtained by frequent injections of ordinary corticotrophin, they point out that

"Corticotrophin zinc phosphate stimulates the adrenal gland for 24 to 48 hours or more after a single injection, as reflected by the eosinophil response and the urinary excretion of 17-ketosteroids, sodium, and potassium. A single injection of 20 I.U. of corticotrophin zinc phosphate has the same effect as four doses of 20 I.U. of ordinary corticotrophin injected 4-hrly".

The action of zinc phosphate corticotrophin on the eosinophil count was found to set in as quickly as that of ordinary corticotrophin, but did not reach a maximum until about 8 hours after the injection and was much more prolonged. *Harry Coke.*

Hamman-Rich Syndrome. Analysis of Current Concepts and Report of Three Precipitous Deaths following Cortisone and Corticotropin (ACTH) Withdrawal. PEABODY, J. W., BUECHNER, H. A., and ANDERSON, A. E. (1953). *Arch. intern. Med.*, **92**, 806. 7 figs, 31 refs.

The authors describe three cases which were regarded as examples of the acute diffuse interstitial fibrosis of the lungs described in 1944 by Hamman and Rich. The duration of symptoms from onset to death was 5½ months, 25 months, and 9 years respectively, and the histological changes, while resembling in every respect those described by Hamman and Rich only in the first case, seemed in the other two to represent a more chronic phase of the same process, consistent with the longer duration of symptoms. In none of the cases was any evidence relevant to the aetiology obtained, either during life or post mortem, and no response to antibiotics was observed. Cortisone or ACTH (corticotrophin) was given in every case. In the first, which was in a relatively acute phase, there was remarkable radiological clearing of the lungs and symptomatic improvement during the administration of the hormones, but shortly after the gradual withdrawal of cortisone there was an acute exacerbation of dyspnoea and cyanosis, with a return of the original *x*-ray appearances, and despite large doses of cortisone and ACTH the patient died within 24 hours of respiratory insufficiency. The second patient also died with severe respiratory difficulty shortly after the end of a 3-week course of cortisone which had produced no objective evidence of improvement. The third patient received moderate doses of ACTH for 27 days, and became very breathless after reduction of the dosage. In spite of reinstitution of treatment with large doses of ACTH together with cortisone, he died of respiratory failure.
J. G. Scadding.

Effects of ACTH on Mental Functions. MALITZ, S., HAMBURG, D. A., and MODELL, S. (1953). *J. nerv. ment. Dis.*, **118**, 315. 36 refs.

The authors, after briefly reviewing previous reports of the effect of ACTH on mental function and in causing behavioural changes, describe an experiment carried out at the Walter Reed Army Medical Center, Washington, D.C., in which eleven unselected young male patients with acute hepatitis, five of whom were receiving ACTH as part of their treatment, were given psychological tests, before treatment began, between the 12th and 18th day (since this appeared to be a period when the effects of ACTH would be at their maximum), and after the end of treatment. The other six patients acted as controls. Each patient was interviewed by a psychiatrist before medication and two or three times per week thereafter, observations being made on the patient's appearance, motor activity, mood, and behaviour. The total dose

of ACTH ranged from 155 to 248 mg. given over periods varying from 2 to 30 days.

The results [which are discussed at a length hardly justified by the very small number of cases] were entirely inconclusive, no definite change being noted in patients before and after treatment with ACTH, nor any difference between these five patients and the six in the control group. The authors therefore conclude that "the strikingly uniform lack of major psychologic changes suggests that the central pharmacologic action of ACTH on the central nervous system has no specific effect on mood and behaviour when administered in the usual clinical dosages". *John C. Kenna.*

Psychiatric Risk from Corticotrophin and Cortisone. LEWIS, A., and FLEMINGER, J. J. (1954). *Lancet*, **1**, 383. 15 refs.

In order to test the thesis that cortisone and corticotrophin (ACTH) should not be given to patients with evidence of psychopathic personality, the authors studied twelve patients at the Maudsley Hospital, London, each of whom had a physical disease which might be relieved by these drugs and had also had an unequivocal mental illness. Eleven of the patients had rheumatoid arthritis and one disseminated lupus erythematosus, and their psychiatric history indicated a severe degree of abnormality, including such conditions as obsessional neurosis, conversion hysteria, schizophrenia, and involutional depression.

After a control period of 6 weeks a placebo was given for 10 days, followed by corticotrophin or cortisone in increasing doses, starting with 40 to 60 mg. of the former and 100 mg. of the latter in 24 hours, until the maximum physical benefit had been obtained, the drug then being withdrawn slowly. The patients' physical condition responded as expected to the drug and relapsed during its withdrawal, while their mental condition improved concomitantly with the physical and relapsed at the same time; in fact the mental improvement seemed to be due to a psychological reaction (normal or hysterical) to the physical improvement rather than to a direct pharmacological effect. The findings of psychological tests before and during treatment provided no decisive evidence of cognitive or emotional changes.

It is concluded, therefore, "that predisposition to develop untoward mental symptoms under treatment with corticotrophin or cortisone cannot be assumed in patients with unstable neurotic personality or a history of mental illness". *Oswald Savage.*

Adrenocortical Function in Burned Patients. With special reference to ACTH and Adrenaline Tests. SEVITT, S. (1954). *Brit. med. J.*, **1**, 541. 7 figs, 20 refs.

The duration of the period of eosinopenia which follows burning was estimated to within $\pm\frac{1}{2}$ day in 35 cases at the Birmingham Accident Hospital, and was plotted against the area of skin burned. The eosinopenia lasted only 1 to 2 days when less than 10 per cent. of the body area was burned, but up to 5 days when larger areas were burned. Eleven patients died during the period of eosinopenia and it is concluded that in these cases the adrenal cortex remained hyperactive until the time of death. In five of the seven other fatal cases there had been an initial period of eosinopenia of normal duration, and there was no other evidence of adrenal failure; in one of the remaining cases the period of eosinopenia had been unduly short.

In twelve out of fourteen patients tested, the response of the eosinophil count to ACTH was normal in the post-eosinopenic period, and the response to adrenaline was likewise normal in nine out of twelve patients tested. In neither of the two patients who responded abnormally to ACTH was the adrenocortical failure thus indicated considered to be serious, since one recovered and the other subsequently developed eosinopenia before death. Two of the three patients who responded abnormally to adrenaline responded normally to ACTH, indicating failure at the hypothalamic-pituitary level rather than adrenocortical failure. These patients were confused and irrational at the time of the abnormal response to adrenaline, the response becoming normal when mental recovery had taken place; it is therefore suggested that the mental disturbance and the lack of response to adrenaline were due to similar changes affecting the cerebral cortex and hypothalamus respectively.

It is recommended that severely burned patients should receive cortisone as soon as evidence of adrenocortical failure, in the form of either a premature return of the eosinophil count to normal or an abnormal eosinophil response to ACTH, is obtained. *C. L. Cope.*

Intra-Articular Hydrocortisone Acetate. (Hydrocortisone-acetaat intraarticulair.) KUIPERS, R. K. W. (1953). *Acta physiother. rheum. belg.*, **8**, 173.

Comparative Observations on the Therapeutic Effect and Tolerance of Cortisone and Hydrocortisone injected intra-articularly in Chronic Joint Disease. (Osservazioni comparative sull'azione terapeutica e sulla tolleranza del cortisone e dell'idrocortisone iniettati nel cavo articolare di artropatici cronici.) ROBECCHI, A., and DANEO, V. (1953). *Reumatismo*, **5**, 368. 9 refs.

Rheumatic Complaints during Chronic Hypercortisonism and Syndromes during Withdrawal of Cortisone in Rheumatic Patients. SLOCUMB, C. H. (1953). *Proc. Mayo Clin.*, **28**, 655.

Capillary Resistance in Rheumatology and Adrenal Cortical Therapy. (La résistance capillaire en rhumatologie et en corticothérapie surrénale.) GALMICHE, P., DUSSY, J., and MAISONDIEU, M. (1953). *Acta physiother. rheum. belg.*, **8**, 137. 14 figs, 28 refs.

Sjögren's Syndrome treated with Cortisone. (Un cas de syndrome de Sjögren traité par la cortisone.) MARAÑÓN, G., and FERNANDEZ Y FERNANDEZ, M. (1953). *Sem. Hôp.* (*Paris*), **29**, 697.

Influence of Diethylstilboestrol associated with Cortisone on Experimental Arthritis in the Adrenalectomized Rat. (Influence du diéthyl-stilboestrol associé a la cortisone sur l'arthrite expérimentale chez le rat surrénalectomisé.) COUTU, L.-L. (1953). *Ann. Endocr.* (*Paris*), **14**, 784. 1 fig., 3 refs.

Researches into the Modifications produced in Synovial Fluid by the Intra-Articular Injection of Hydrocortisone Acetate and Cortisone. (Ricerche sulle modificazioni del liquido sinoviale di artropatici determinate da iniezioni intra-articolari di idrocortisone acetato e di cortisone.) DANEO, V., and FILOGAMO, G. (1954). *Reumatismo*, **6**, 123. 1 fig., 11 refs.

Serious Untoward Gastro-Intestinal Manifestations possibly related to Administration of Cortisone and Corticotropin. SAUER, W. G., DEARING, W. H., and WOLLAEGER, E. E. (1953). *Proc. Mayo Clin.*, **28**, 641.

Certain Psychodynamic Aspects of the Role of Cortisone and Allied Substances in the Production of Psychologic Responses. ROME, H. P. (1953). *Proc. Mayo Clin.*, **28**, 649. 9 refs.

Treatment of Rheumatism with Steroids. (Tratamiento del reumatismo por los esteroides.) MORENO, A. R. (1953). *Arch. argent. Reum.*, **16**, 117.

Preliminary Trials of Combined Treatment with Cortisone and Diacetylpyrocatchol Carboxylic Acid in Rheumatic Diseases. (Premiers essais avec l'association Cortisone-Acide diacétylpyrocatéchol carboxylique dans les affections rhumatismales.) ORY, M. (1954). *Brux.-méd.*, **34**, 921.

Effect of ACTH and Cortisone on the Blood Pyruvic Acid Level. [In English.] GITELSON, S. (1954). *Acta endocr.* (*Kbh.*), **15**, 225. 4 figs, 33 refs.

Other General Subjects

A Claim to Fame: Thomas Sydenham. STEWART, J. S. (1953). *Post-grad. med. J.*, **29**, 465. 6 refs.

Sydenham is introduced as one who practised medicine first and foremost as an art—the "quiet art" of Virgil's physician. To this end he set out to collect "as genuine and natural a description or history of all diseases as can be procured". His attempt at a definition of disease is considered to show a greater insight into the essence of the matter than some current definitions of ill-health:

> A disease, in my opinion, how prejudicial soever its causes may be to the body, is no more than a vigorous effort of nature to throw off the morbific matter, and thus recover the patient.

Sydenham's greatest claim to fame are his observations on the natural history of disease and his devotion to the cure of the patient. Born in 1624 of Puritan stock, he went to Oxford at the age of 18, but soon left to serve, first as a trooper and later as a captain, in the Parliamentary army. In 1647 he returned to Oxford to study medicine, being created Bachelor of Medicine by the Chancellor after only 6 months' study—an irregular procedure even at that time. He later studied under Barbeyrac at Montpellier, and after practising for some time in London became a Licentiate of the Royal College of Physicians. He was never elected to the Fellowship, but whether this was for political reasons or through personal animosity is not clear. He was highly regarded by many of his greatest contemporaries and was a personal friend of Robert Boyle and John Locke. Dr. Andrew Brown, a Scottish physician, and Thomas Dover, of Dover's powder fame, were two of his medical disciples. Dover, who was Sydenham's patient as well as pupil, has described how his smallpox was treated by a cooling regimen, with no fire, open windows, and few bedclothes, and twelve bottles of small beer every 24 hours.

Sydenham substituted faithful observation and accurate note-taking at the bedside for speculation and dogma. His achievement in medicine may be compared to that of his friend Locke in philosophy. Opinion among physicians was at first divided, but gradually turned in Sydenham's favour, especially during the 18th century. On the Continent his reputation was greater than in his own country, and the renowned Hermann Boerhaave is said to have taken his hat off whenever he mentioned the name of the "English Hippocrates". His achievements included the introduction of a tincture of opium, the cooling treatment of smallpox, and the use of Peruvian bark in quartan agues. He described the rheumatic type of chorea, recorded his own sufferings from gout, and left classic descriptions of smallpox, measles, and scarlet fever. His abiding fame rests chiefly on his "natural history" method in the study of disease—especially epidemic disease—and his advocacy of practical bedside medicine.

The study of Sydenham and his work calls to mind the dual nature of medicine. While his great contemporary Harvey stands out primarily as a man of science, Sydenham must be regarded as one who practised the art of medicine. This is not to suggest that he made no use of scientific methods, but it explains how his devotion to immediate needs meant that much that was best in him died with him. He has been well described by Major as "the greatest representative of the practical medicine of practical England". *W. J. Bishop.*

Preliminary Results of Treatment of Various Rheumatic Conditions with Large Doses of Vitamin B_{12}. (Primeros resultados obtenidos en el tratamiento de algunos sindromes reumaticos con grandes dosis de vitamina B_{12}.) BARCELÓ TORRENT, P., ALEGRE MARCET, C., CASADEMONT, M., and VERGES, G. (1953). *Rev. esp. Reum.*, **5**, 119. 11 refs.

Conditions clinically confused with the Rheumatic State. SASLAW, M. S., HERNANDEZ, F. A., and WERBLOW, S. C. (1954). *J. Pediat.*, **44**, 414. 1 ref.

Skin and Peripheral Circulation in Rheumatic Diseases. (Hautsegment und periphere Blutzirkulation bei rheumatischen Erkrankungen.) JOSENHANS, G. (1954). *Dtsch. med. Wschr.*, **79**, 505. 21 refs.